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# CHANGES IN THE ARTERIES IN THE WALLS OF TUBERCULOUS PULMONARY CAVITIES

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The purpose of this communication is to report certain observations made on the anatomic changes of the pulmonary arteries and their branches in the walls of tuberculous cavities and in the pulmonary parenchyma adjacent to them. The possible prognostic significance of these arterial changes in reference to the healing of the cavities is discussed.

## MATERIAL AND METHODS

The material studied consists of 30 cases in which tuberculous cavities were examined at necropsy. During life frequent roentgenograms of the chest were made, and the behavior of the cavities as well as of the surrounding tuberculous lesions was noted. Seven of these patients received artificial pneumothorax. The arterial changes about the partially collapsed cavities were especially noted.

The method of study in each case was as follows: A postmortem roentgenogram of the chest was made. The lungs and heart were removed in one mass. From 300 to 400 cc. of 50 per cent barium sulfate suspended in water was injected into the pulmonary arterial system through the conus arteriosus. After the arteries were filled, air was pumped into the bronchi, thus inflating the cavities. The specimen was laid on a casette containing a roentgen film and an exposure made using these factors: 100 prereading kilovolts, 75 milliamperes, 1/20 second exposure time and a distance of 4 feet (122 cm.). By this method it is possible to obtain a composite picture of the arterial changes around the cavities. Following the arteriographic study, the specimen was dissected to observe the gross changes of the arteries in the walls of the cavities and areas adjacent to them. Whether the tuberculous process was predominantly fibrotic or caseous was carefully noted in each case. Sections were taken from the walls of the cavities and adjacent pulmonary parenchyma for histologic examination.

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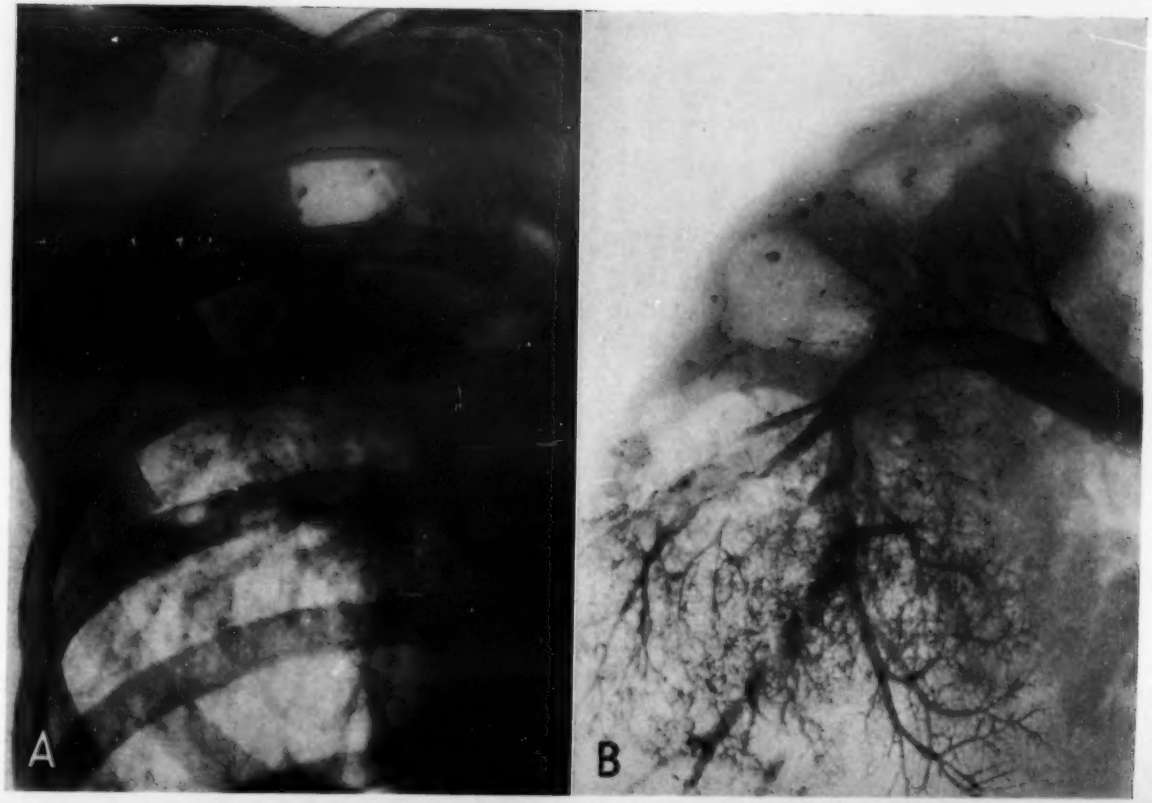


Fig. 1.—*A*, roentgenogram of the chest of a white woman aged 27. Pulmonary tuberculosis had been present for five years. Three cavities may be noted in the upper lobe of the right lung, with calcified tubercles in the cavity walls. *B*, arteriogram. Note absence of blood vessels throughout the entire lobe and marked narrowing of the first and second main branches of the right pulmonary artery.

cavity walls. *B*, arteriogram. Note absence of blood vessels throughout the entire lobe and marked narrowing of the first and second main branches of the right pulmonary artery.



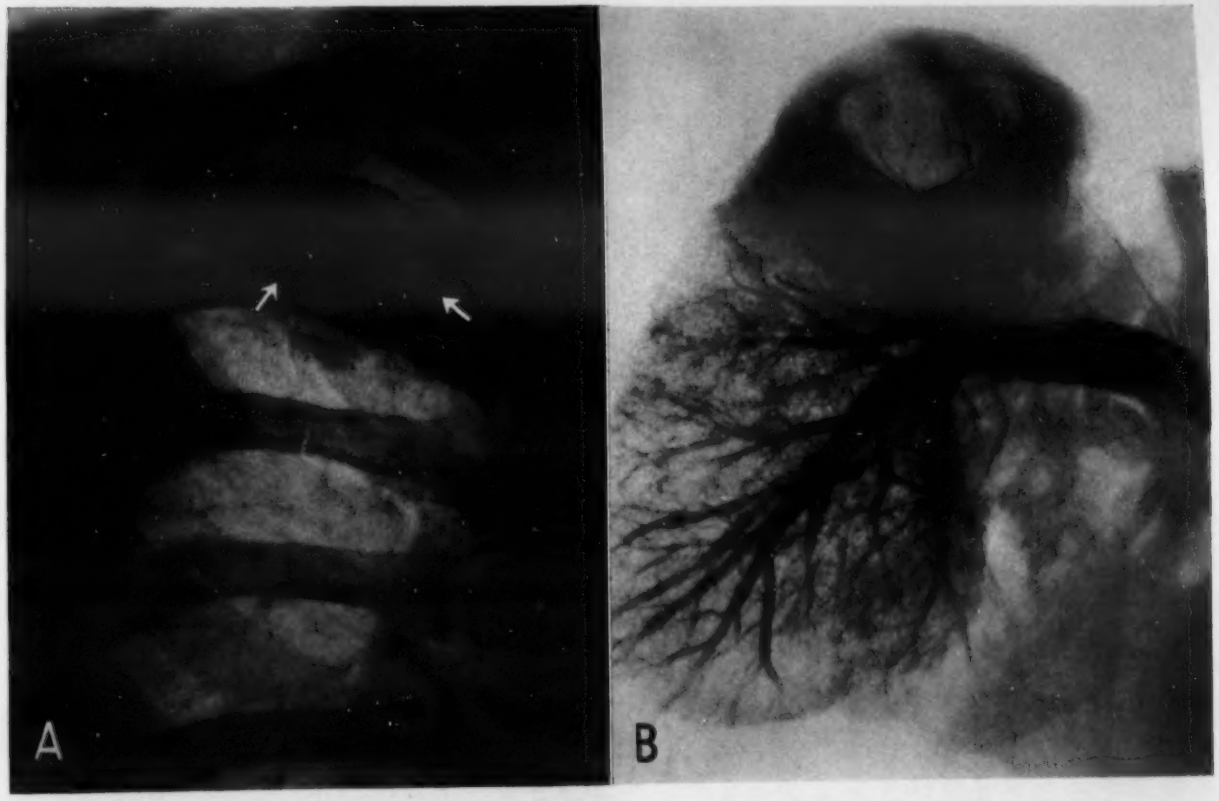


Fig. 2.—*A*, roentgenogram of the chest of a white woman aged 22. She had been ill with pulmonary tuberculosis for two years. A cavity may be seen in the right apex with no evidence of fibrosis about it. *B*, arteriogram. Note the abundance of blood vessels around the cavity in contradistinction to the absence of vessels in figure 1 *B*.

RESULTS

The most frequently involved branch of the pulmonary artery around a tuberculous cavity is the first main branch, which extends upward, supplying the upper lobe of the lung. This branch comes off the main trunk approximately at the level of the second rib anteriorly at the parasternal line, and it shows marked differences in size, length and number of branches in different persons. In some cases the first branch comes off as a single vessel and extends into the upper lobe for a considerable distance before it divides into several smaller branches. In others it divides into three or more branches as soon as it leaves the main trunk.

The outstanding findings in the wall of the cavity are the destruction of capillaries and arterioles and the marked narrowing of the larger arteries. These changes are most marked in cases of fibroid tuberculosis with a duration of illness of over five years (fig. 1). Within the fibrotic areas the arterioles are completely occluded. Many of the small branches are entirely destroyed by cavitation. The larger branches are narrowed on account of a sclerotic process about the perivascular tissues and also within the vessels themselves. On the contrary, arterial sclerosis is not marked about the cavities of recent origin with a duration of illness of less than a year and without much fibrosis (fig. 2). In such acute cavities, when the tuberculous material has been expectorated, the inner walls of the cavities, instead of being relatively smooth and fibrotic, are often shaggy and friable, owing to the presence of pulmonary tissues without fibrosis and a considerable amount of granulation tissue. In such cases the arteriograms showed excellent vascularization of the walls of the cavities. The terminal ends of the pulmonary arteries extend to the inner surface of the cavities. These cavities often contain sputum well mixed with blood, giving the sputum a reddish chocolate color. Erosion of such superficial vessels may readily produce hemoptysis of varying severity. The pulmonary tissue surrounding these cavities shows acute consolidation with marked congestion. In all cases the portion of the cavity most devoid of blood vessels is that part adjacent to the thoracic wall (fig. 3). In none of the cases studied was there any evidence of a pulmonary artery supplying that part. This is particularly true in cases with considerable fibrosis. Small capillaries found on the outer surface of the wall are the terminal portions of the intercostal vessels supplying the adherent pleura.

At the bottoms and at the medial walls of the cavities the most common findings are marked narrowing and thrombosis of the arteries. In 1 case the entire right lung was hollowed out, and there was marked destruction of the pulmonary artery. An old antemortem thrombus prevented possible fatal hemorrhage (fig. 4).

Marked fibrosis of the stumps of the first branch of the pulmonary artery is common (fig. 3). Such stumps are often embedded in the

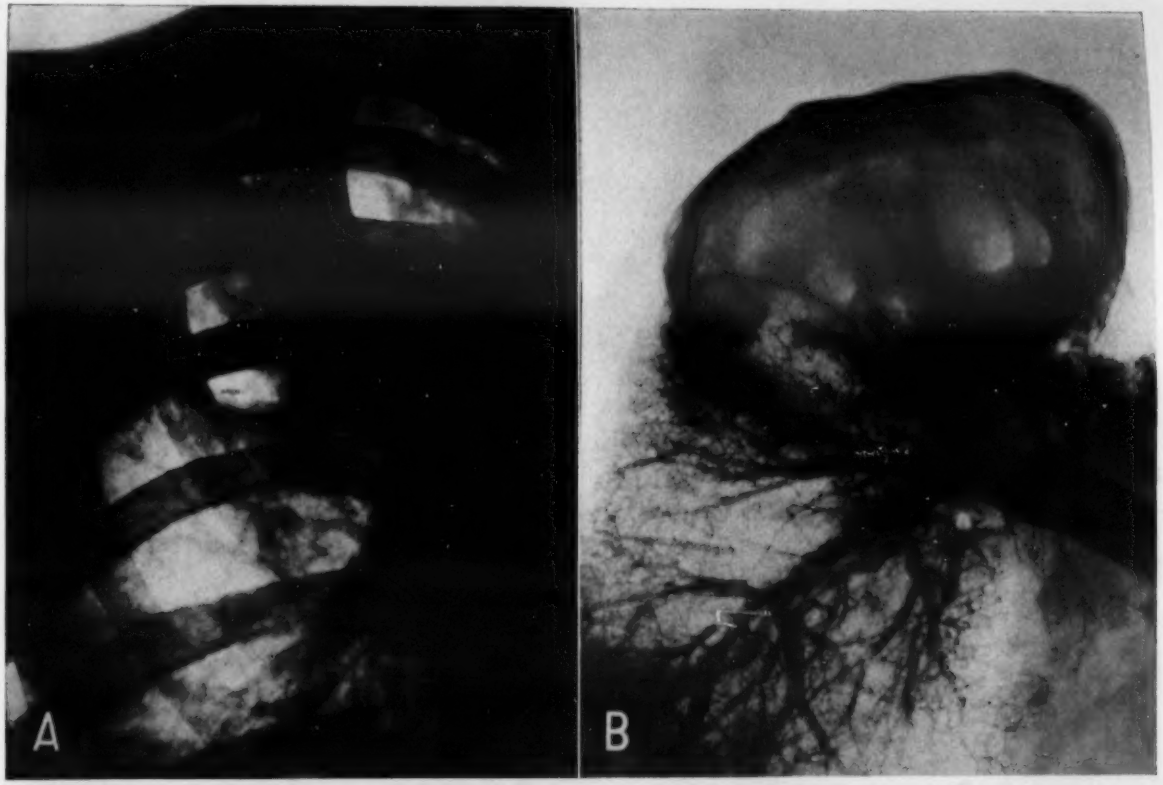


Fig. 3.—*A*, roentgenogram of the chest of a white woman aged 26. Pulmonary tuberculosis had been present for five years. A large cavity may be seen in the upper lobe of the right lung, with fibrosis around the cavity. *B*, arteriogram. Note the marked sclerosis of the first and second main branches of the right pulmonary artery and the absence of blood vessels in the peripheral portion of the cavity wall.

Fig. 4.—*A*, roentgenogram of the chest of a white man aged 45. He had had pulmonary tuberculosis for two years. The entire upper lobe of the right lung is excavated. *B*, arteriogram. Note thrombosis of the eroded stump of the first main branch of the right pulmonary artery. The stump is buried in fibrous tissue.

stump of the first main branch of the right pulmonary artery. The stump is buried in fibrous tissue.



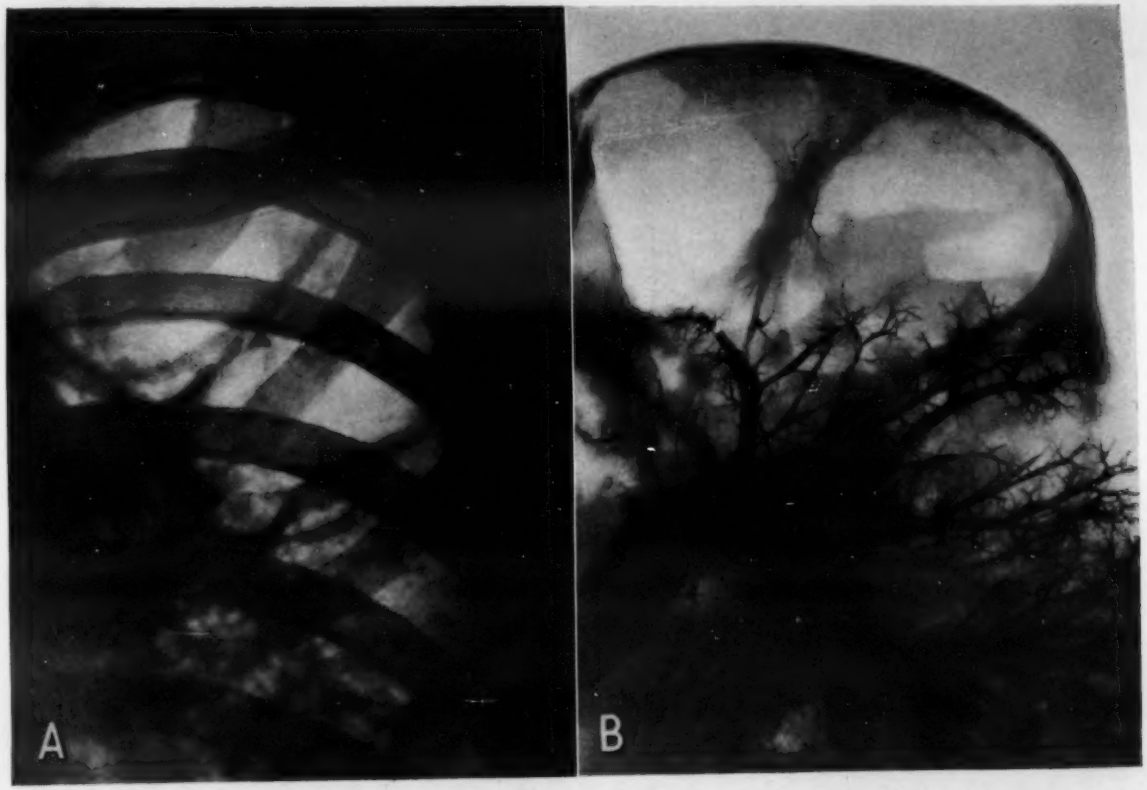


Fig. 5.—*A*, roentgenogram of the chest of a white man aged 20. Pulmonary tuberculosis had been present for one year. A large cavity may be seen in the upper lobe of the left lung, with trabeculae crossing the cavity. *B*, arteriogram. Note the arteries within the trabeculae. Erosion of such vessels may cause hemoptysis.

fibrous tissue forming the wall of the cavity. With extension of the disease, the fibrous tissue covering the stumps becomes eroded, exposing the vessels. When this occurs, the involved vessels dilate and eventually rupture, causing massive hemoptysis.

In the trabeculae crossing the cavities, the blood vessels are frequently occluded by thrombosis. When this does not occur, patent pulmonary arterial branches are occasionally found in these trabeculae (fig. 5). Sudden rupture of such vessels may give rise to serious hemorrhage.

About the acute pneumonic areas without caseation the capillaries as well as the arterioles dilate. In cases with small honeycombed cavitation near the periphery of the lung, the consolidated areas intervening between the cavities show marked congestion (fig. 6). The pleura overlying such areas shows histologic evidences of pleuritis. Such areas may play a part in the development of pleural effusions with or without tubercle bacilli in the fluid.

Seven of the patients received artificial pneumothorax. Within the relatively normal portion of the collapsed lung, even after extensive collapse for three years, practically no pathologic changes in the pulmonary arteries are noted. However, within the tuberculous regions the arteries show marked narrowing and in many cases thrombosis. As the lung becomes smaller because of collapse, the arteries become much shorter and somewhat narrower, but there is no actual kinking of the vessels unless the lung is entirely collapsed under hydropneumothorax. The arteries about the cavities in the collapsed lung show the same type of changes as those in the noncollapsed lung, but to a lesser degree. In a few cases the collapse of the cavities was marked by close apposition of the walls of the cavities, but bridging across of cavities by new fibrous tissue was not noted.

In 1 case the tuberculous cavity in the upper lobe of the left lung was observed for a year, and then artificial pneumothorax was instituted. Following this the cavity gradually became smaller, and finally it could not be seen in the roentgenogram. After three years of the pneumothorax treatment, this patient died of extrapulmonary abscesses. At autopsy the site of the cavity revealed a small opening, not larger than 2 to 3 mm. in diameter. The histologic examination of the cavity wall showed crinkling through purse string–like constriction of the newly formed fibrous tissue outside the actual wall of the cavity. There were numerous blood vessels both within and without this outer ring of fibrous tissue (fig. 7). The decrease in the size of this cavity was from all directions. There was no actual flattening of the cavity.

Fig. 6.—*A*, roentgenogram of the chest of a white man aged 27. Acute pulmonary tuberculosis had been present for one year. Scattered small cavities may be seen throughout the entire upper lobe of the right lung. *B*, arteriogram. Note the dilatation of the arterioles in the consolidated area between the cavities in the extreme apex of the upper lobe.

COMMENT

The role of the pulmonary vascular system in chronic pulmonary diseases is probably of greater importance than has been generally realized. This is particularly true in connection with chronic pulmonary tuberculosis. In Europe and Argentina the pulmonary arterial circulation has been studied in living patients by various investigators.[1] These observers outlined the pulmonary artery and its branches by injecting sodium iodide into the circulations of normal subjects and patients with pulmonary and cardiac disease. In general, a decrease in pulmonary arterial circulation in tuberculous areas and a suppression in circulation in lungs collapsed by pneumothorax have been noted. Detailed observations on the type and degree of the circulatory changes have not been recorded.

In this country, Brenner [2] has carried out postmortem studies on the histologic changes occurring in the arteries of the lungs. He found frequent involvement of the walls of the larger arteries and endarteritis obliterans of the smaller arterioles in chronic tuberculosis. Birkelo and Brosius [3] have described certain differences in the circulatory changes in various forms of tuberculosis by means of arteriographic studies. Rupture of the pulmonary artery producing fatal hemoptysis was investigated by Lipstein,[4] Auerbach,[5] Bogen [6] and in our earlier study.[7] Wood and Miller [8] employed the arteriographic method in outlining the bronchial arteries and found dilatation of the bronchial vessels in tuberculous areas where destruction of the pulmonary arterial bed had occurred. Most of their cases were fairly recent, with practically no old fibrotic cavities similar to those studied in our series. Robb and

1. Lopa de Carvalho; Egas Moniz, and Almeida Lima: Presse méd. **40**: 1098, 1932. Egas Moniz; Lopa de Carvalho, and Almeida Lima: ibid. **39**:996, 1931. de Carvalho, L., and de Carvalho, A.: Rev. de la tuberc. **1**:578, 1935. Hinault, V.: J. de méd. de Paris **57**:842, 1937. Ameuille, P.; Ronneaux, G.; Hinault, V.; Desgrez, H., and Lemoine, J. M.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:729, 1935. Laubry, C.; Cottenot, P.; Routier, D., and Heim de Balzac, R.: J. de radiol. et d'électrol. **19**:193, 1935. Hinault, V., and Desgrez, H.: Rev. de la tuberc. **2**:936, 1936. Ameuille, P.; Ronneaux, G.; Hinault, V., and Desgrez, H.: J. de radiol. et d'électrol. **22**:97, 1938. de Carvalho, L., and Rocheta, J.: Presse méd. **42**:2057, 1934. Bosco, J. J.; Fierro, L. L., and Roseles, E. A.: Rev. méd. del Rosario **28**:68, 1938.

2. Brenner, O.: Arch. Int. Med. **56**:228, 1935.

3. Birkelo, C. C., and Brosius, W. L.: Radiology **21**:261, 1938.

4. Lipstein, S.: Quart. Bull., Sea View Hosp. **2**:416, 1937.

5. Auerbach, O.: Am. Rev. Tuberc. **39**:99, 1939.

6. Bogen, E.: Am. J. Clin. Path. **2**:299, 1932.

7. Charr, R., and Savacool, J. W.: Am. J. M. Sc. **199**:641, 1940.

8. Wood, D. R., and Miller, M.: J. Thoracic Surg. **7**:649, 1938.

Steinberg [9] have recently investigated the main pulmonary circulation in living patients by injections of diodrast. There are as yet no reports of studies on tuberculous patients by this method, but presumably the results would be similar to those with the sodium iodide technic.

Healing of tuberculous lesions as evidenced by autopsy material showed extensive formation of fibrous tissue leaving a dense scar at the site of the disease (Pinner [10]). Pagel and Simmonds [11] stated that the factors chiefly responsible for the healing of tuberculous cavities are (1) the formation of nonspecific granulation tissue and caseous material to fill the cavity, (2) fibrosis of the open cavity and (3) fibrosis and calcification of the contents of the cavity. Bronchial occlusion by kinking, stenosis or pressure from without may also play a part.

Filling of the cavity by nonspecific granulation tissue, fibrosis of the cavity and calcification of the caseous material require an adequate blood supply. In a large measure, healing of tubercles or tuberculous cavities is the same as healing of any wound in that formation of fibroblasts plays an important part. For the growth of fibroblasts, an adequate supply of blood is imperative. It is generally recognized that the pulmonary parenchyma per se does not regenerate. Therefore, in cavity healing it is the formation of granulation tissue which may be significant.

In figure 7 are illustrated a tuberculous cavity and what appears to be the mode of healing. The crinkling of the wall of the cavity was produced by the constricting action of the circular band of fibrous tissue. It has been pointed out that there were numerous blood vessels within and without the zone of new fibrous tissue. The decrease in the size of the cavity was from all directions.

In connection with this case of healing of a cavity, we have reviewed the histories of some 30 patients who have received pneumothorax for one to ten years and are now working without symptoms. In all of these the decrease in the size of the cavities as evidenced in the serial roentgenographic studies was from all directions. One may surmise that the healing process in such patients may have been somewhat akin to that seen in figure 7. If so, these well patients must have had good blood supply about their tuberculous regions. It has been shown by arteriograms that the relatively acute caseous tuberculous regions have fairly good blood supply. When the caseous material is expectorated, the wall of the cavity may reveal numerous small blood vessels (fig. 2). The patients in whom pneumothorax was satisfactory might have had lesions of this type.

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9. Robb, G. P., and Steinberg, I.: J. A. M. A. **114**:474, 1940.

10. Pinner, M. J.: Alexander's Collapse Therapy of Pulmonary Tuberculosis, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

11. Pagel, W., and Simmonds, F. A. H.: Am. J. M. Sc. **197**:281, 1939.

Fig. 7.—This is a low magnification of a cross section of an almost completely healed cavity. Note the shrinking of the cavity, probably due to constriction of the ring of newly formed fibrous tissue surrounding the cavity.

It is generally regarded that thick-walled cavities do not respond well to pneumothorax. When penumothorax is "pushed" under positive pressure, the cavity begins to flatten from side to side, but there is no general and even decrease of its size. In such a case the postmortem arteriograms showed very marked fibrous tissue formation about the cavity with extensive fibrosis and thrombosis of all the blood vessels near the cavity.

It is therefore suggested that the difference in response to collapse therapy between the old, fibrous cavity and the recent, thin-walled cavity may be dependent to a certain extent on the blood supply of the wall of the cavity. This factor should be borne in mind in the application of collapse measures for tuberculous cavities, certainly in expressing the prognosis.

There is at present no satisfactory method of determining the vascular changes about tuberculous cavities. Various roentgenographic studies made on living patients using a radio-opaque substance fail to show the condition of the vessels within the diseased areas. Planographic examinations demonstrate the large pulmonary vessels but fail to show the smaller vessels in the tuberculous regions. Until some technic is perfected, one has to be guided by the duration of the disease and the general roentgenographic appearances in estimating the extent of pulmonary arterial changes about the tuberculous cavities.

SUMMARY

Pulmonary arterial changes around tuberculous cavities were studied in 30 cases by postmortem arteriographic and gross and histologic examinations.

The most freqeuently involved artery in pulmonary tuberculosis is the first main branch of the pulmonary artery, which lies at about the level of the second rib anteriorly at the parasternal line. Destruction of capillaries and sclerosis of arterioles about the cavities are frequent. These changes are most extensive around fibroid cavities of long standing. About the cavities of recent origin, without fibrosis, arterial changes are less marked. The peripheral portions of the cavities adjacent to the chest wall are most devoid of arterial supply.

In our series of cases in which pneumothorax was satisfactory the decrease in the size of the cavity was concentric, probably because of purse string–like constriction of the cavity by young fibrous tissue outside the wall of the cavity.

One may conclude that a possible relationship exists between the arterial supply of the lung tissue surrounding a tuberculous cavity and its healing.

# EFFECT OF EXPOSURE TO HIGH OXYGEN TENSION ON THE LUNGS AND HEART OF THE RAT

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It is well known that oxygen poisoning may be regularly induced in animals by prolonged exposure to high oxygen tension. This may be accomplished by exposure to air at high barometric pressure [1] or to high oxygen concentrations at normal barometric pressure.[2] The attendant pathologic changes occurring in the animals have been studied by numerous investigators and characteristic pulmonary changes described. Smith and co-workers [3] described sclerotic changes in the pulmonary arteries and arterioles of rats following prolonged exposure to an environment of compressed air having an oxygen tension of approximately 635 mm. of mercury. Bennett and Smith [4] demonstrated pulmonary arterial hypertension in rats exposed in the same manner, and they described progressive sclerotic changes in the pulmonary arterioles and arteries commencing as early as the third day of exposure. The latter studies were made on rats continuously exposed for periods ranging up to thirty-eight days. Progressive or regressive changes occurring in the pulmonary vessels after discontinuance of the exposure were not investigated.

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From the Institute of Pathology, Western Reserve University.

This study was aided by a grant from the Josiah Macy Jr. Foundation.

1. Smith, J. L.: J. Physiol. **24**:19, 1899. Hill, L., and MacLeod, J. J. R.: ibid. **29**:492, 1903. Bornstein, A., and Stroink: Deutsche med. Wchnschr. **38**:1495, 1912. Smith, F. J. C.; Heim, J. W.; Thomson, R. M., and Drinker, C. K.: J. Exper. Med. **56**:63, 1932.

2. Adams, A.: Biochem. J. **6**:297, 1912. Karsner, H. T.: J. Exper. Med. **23**:149, 1916. Barach, A. L.: Am. Rev. Tuberc. **13**:293, 1926. Binger, C. A. L.; Faulkner, J. M., and Moore, R. T.: J. Exper. Med. **45**:849, 1927. Achard, C.; Binet, L., and LeBlanc, A.: Compt. rend. Acad. d. sc. **184**:771, 1927.

3. Smith, F. J. C.; Bennett, G. A.; Heim, J. W.; Thomson, R. M., and Drinker, C. K.: J. Exper. Med. **56**:79, 1932.

4. Bennett, G. A., and Smith, F. J. C.: J. Exper. Med. **59**:181, 1934.

The present investigation was prompted by the importance of knowing whether or not sclerotic changes in arterial vessels produced by an initial injury may be progressive, regressive or static. The method selected for the production of this injury was the exposure of animals to a high oxygen concentration at normal rather than increased barometic pressure.

A glass and metal chamber, capacity 0.5 cubic meter, was so designed as to accommodate a large number of adult rats supplied with sufficient food and water to last several days. A glass top permitted observation of the animals during exposure. During the acute experiment the chamber was sealed except for a single outflow vent, and the air within was replaced by a rapid inflow of gas from tanks with the desired oxygen content. A very slow inflow from the tanks was maintained thereafter, and the gas within the chamber was continuously reconditioned by successive passages through sodium hydroxide solution, lime N. F. (quicklime), sulfuric acid and water in a completely closed system. With this system the percentage of oxygen and the humidity within the chamber were maintained constant. A constant temperature was obtained by regulation of the room temperature.

The chamber was operated continuously for twenty-eight days except for six occasions when the circulation was stopped and the chamber opened for cleaning, introduction of food and water or introduction or removal of animals. The gas prepared for the experiment was a mixture of oxygen and air having an oxygen content of 85 per cent. Frequent determinations of oxygen and carbon dioxide were made on the gas within the system, the syringe method of Henderson and Greenberg [5] being used. The average percentage of oxygen during the experiment was 83, with fluctuation from 80 to 85. The carbon dioxide content was at all times less than 0.5 per cent. The average relative humidity was 49 per cent, with fluctuation from 40 to 60 per cent. The average temperature was 27 C., with fluctuation from 26 to 28 C.

The rats used were all females of albino stock, approximately 6 months old. Sixteen were introduced into the chamber on the first day of the experiment, the survivors receiving twenty-eight days of exposure. Groups of 16 and 18 additional animals were introduced on the fourteenth and twenty-first days, respectively, the survivors receiving fourteen and seven days of exposure, respectively.

Animals that died or were killed were examined as soon as possible after death and the organs placed in a 4 per cent solution of formaldehyde. Attempts to determine pulmonary arterial blood pressures by the direct manometric method prior to killing the animals were unsatisfactory. All lungs were studied histologically. All hearts, after prolonged fixation, were dissected, and the weights of the left and right ventricles obtained by the method of Rytand and Dock.[6]

## PULMONARY CHANGES

*Fourth Day of Exposure.*—Nine animals that died or were killed on the fourth day of exposure showed bilateral hydrothorax with partial collapse of the lungs. Histologically all showed within the alveoli a gen-

5. Henderson, Y., and Greenberg, L. A.: J. A. M. A. **96**:1474, 1931.

6. Rytand, D. A., and Dock, W.: Arch. Int. Med. **56**:511, 1935.

eralized exudate of fluid, fibrin and a few mononuclear and polymorphonuclear cells. The alveolar capillaries were engorged, and the cells lining the alveoli were enlarged. There was a striking perivascular exudate of fluid, large and small mononuclear cells and scattered polymorphonuclear neutrophils and eosinophils. Young fibroblasts and newly formed capillaries were present in the perivascular areas. The same changes were present in the peribronchial areas. The arteries and arterioles showed edema of the media and adventitia, which was slight in most instances. Five of the 9 animals showed a few areas of bronchitis characterized by bronchial and dense peribronchial infiltrations of lymphocytes and polymorphonuclear leukocytes.

*Seventh Day of Exposure.*—Three animals dead on the seventh day of exposure showed no fluid in the pleural cavities. There was less intra-alveolar and perivascular exudate than was seen in animals on the fourth day of exposure, and the perivascular exudate showed more advanced organization. Most small arteries and arterioles showed no definite change, but an occasional vessel showed medial edema and areas of hyaline change. Each animal showed areas of bronchitis similar to that seen in the animals on the fourth day of exposure.

*Fourteenth Day of Exposure.*—Three animals dead on the fourteenth day of exposure and 2 dead on the sixteenth day did not show the generalized intra-alveolar and perivascular exudate seen in the animals on the fourth and seventh days of exposure. However, they showed more severe suppurative bronchitis with varying degrees of bronchiectasis. In addition, there were large areas of bronchopneumonia characterized by a dense intra-alveolar exudate of polymorphonuclear leukocytes. The arterioles and smallest arteries showed no definite changes except for slight thickening of the walls of an occasional vessel and occasional foci of hyaline change. There was a condensation of new adult connective tissue around the adventitia of larger arteries.

*Twenty-First Day of Exposure.*—Two animals dead on the twenty-first day of exposure showed no change in arteries or arterioles other than that seen in animals on the fourteenth day of exposure. One animal, R-11, showed generalized pulmonary edema but no suppurative disease. The other showed suppurative bronchitis, bronchiectasis and bronchopneumonia.

*Twenty-Eighth Day of Exposure.*—Three animals exposed for twenty-eight days and dead on the thirtieth and forty-first days showed extensive bronchopneumonia with abscesses, bronchiectasis and emphysema. The arteries and arterioles showed only the slight changes seen in previous animals.

*Changes After Survival Periods of Seven to Fifteen Months.*—From seven to fifteen months after exposure autopsies were made on 5 animals exposed for fourteen days, 8 exposed for seven days and 1 exposed for twenty-eight days. In these animals no noteworthy changes were found in the arteries or arterioles except for a possible increase in the collagenous tissue of the adentitia of larger vessels. These animals showed

TABLE 1.—*Ventricle and Body Weight Ratios of Rats During the Acute Experiment*

| Rat | Exposure | Died | RV:LV | RV:B | LV:B |
|---|---|---|---|---|---|
| | | | Group 1 | | |
| P- 4 | 4 days | 4th day | 0.3768 | 0.00076 | 0.00203 |
| P-12 | 4 days | 4th day | 0.4640 | 0.00092 | 0.00199 |
| P-18 | 4 days | 4th day | 0.4000 | 0.00076 | 0.00190 |
| P-21 | 4 days | 4th day | 0.4632 | 0.00107 | 0.00231 |
| P-25 | 4 days | 4th day | 0.4019 | 0.00082 | 0.00204 |
| P-33 | 4 days | 4th day | 0.4272 | 0.00078 | 0.00185 |
| R- 2 | 4 days | 4th day | 0.4412 | 0.00087 | 0.00198 |
| R-13 | 4 days | 4th day | 0.3617 | 0.00078 | 0.00218 |
| P-32 | 4 days | 4th day | 0.3985 | 0.00087 | 0.00219 |
| | | Mean | 0.4149 ± 0.0342 S.D. | 0.000847 ± 0.000094 S.D. | 0.002052 ± 0.000139 S.D. |
| | | | Group 2 | | |
| R- 7 | 7 days | 7th day | 0.4609 | | |
| R- 4 | 7 days | 7th day | 0.5290 | | |
| R-16 | 7 days | 7th day | 0.6286 | 0.00160 | 0.00254 |
| R- 8 | 14 days | 14th day | 0.5181 | | |
| P-15 | 14 days | 14th day | 0.5131 | 0.00101 | 0.00197 |
| R-14 | 14 days | 14th day | 0.7704 | 0.00172 | 0.00223 |
| P-16 | 14 days | 16th day | 0.5455 | 0.00124 | 0.00228 |
| P-11 | 14 days | 16th day | 0.6137 | 0.00150 | 0.00245 |
| R-12 | 21 days | 21st day | 0.5162 | 0.00116 | 0.00226 |
| R-11 | 21 days | 21st day | 0.8417 | 0.00214 | 0.00254 |
| P-17 | 7 days | 25th day | 0.5095 | | |
| R- 3 | 28 days | 30th day | 0.7497 | 0.00180 | 0.00240 |
| R- 9 | 28 days | 30th day | 0.5081 | 0.00146 | 0.00289 |
| R-10 | 28 days | 41st day | 0.6709 | 0.00176 | 0.00262 |
| | | Mean | 0.5982 ± 0.1135 S.D. | 0.00154 ± 0.00032 S.D. | 0.002418 ± 0.000237 S.D. |

Using group 1 as the control group, by the method of Fisher [7] for the difference between the means of RV:LV in the two groups t = 4.50, and at the 1 per cent level this is statistically significant. For the difference between the means of RV:B in the two groups t = 6.71, and at the 1 per cent level this is statistically significant. For the difference between the means of LV:B in the two groups t = 3.77, and at the 1 per cent level this is statistically significant.

RV = weight of right ventricle.
LV = weight of left ventricle.
B = body weight.

chronic bronchitis, bronchopneumonia and varying degrees of bronchiectasis and emphysema. Control animals showed the same type of chronic inflammatory change, the extent of involvement appearing to be comparable to that in the experimental animals.

## CARDIAC HYPERTROPHY

As shown in table 1, the hearts of animals dead or killed on the fourth day of exposure were used as controls. In the group on which autopsies were made seven to forty-one days after the beginning of

7. Fisher, R. A.: Statistical Methods for Research Workers, ed. 5, London, Oliver & Boyd, 1934.

exposure there was a significant increase in the mean ratio of right ventricular weight to left ventricular weight. An even more significant increase in the mean ratio of right ventricular weight to body weight was found. The mean ratio of left ventricular weight to body weight showed only a slight increase.

In the group of animals on which autopsies were made seven to fifteen months after exposure (table 2) there was an increase in the mean ratio of right ventricular weight to left ventricular weight, but its statistical significance was slight. The body weights at death of 7 of these animals were not known, so that no fair evaluation of the ratio of ventricular weight to body weight in this group could be made.

TABLE 2.—*Ventricle and Body Weight Ratios of Rats After Prolonged Periods Following Exposure*

| Rat | Exposure | Died | RV:LV | RV:B | LV:B |
|---|---|---|---|---|---|
| | | Group 3 | | | |
| P- 7 | 14 days | 15th mo. | 0.4507 | 0.00106 | 0.00237 |
| P- 3 | 14 days | 13th mo. | 0.7112 | | |
| P- 2 | 14 days | 15th mo. | 0.6451 | 0.00145 | 0.00240 |
| P-13 | 14 days | 15th mo. | 0.3413 | 0.00075 | 0.00220 |
| P-10 | 14 days | 9th mo. | 0.7453 | | |
| P-27 | 7 days | 13th mo. | 0.4108 | 0.00080 | 0.00196 |
| P-34 | 7 days | 7th mo. | 0.4840 | | |
| P-26 | 7 days | 9th mo. | 0.6011 | | |
| P-22 | 7 days | 7th mo. | 0.5990 | | |
| P-28 | 7 days | 14th mo. | 0.6205 | | |
| P-30 | 7 days | 10th mo. | 0.6447 | 0.00223 | 0.00346 |
| P-31 | 7 days | 13th mo. | 0.7210 | | |
| P-29 | 7 days | 15th mo. | 0.3922 | 0.00073 | 0.00187 |
| R-15 | 28 days | 8th mo. | 0.7276 | 0.00159 | 0.00218 |
| | | | Mean 0.57817 ± 0.13256 S.D. | | |

By the method of Fisher,[7] using group 1, table 1, as the control, for the difference between the means of RV:LV in the two groups t = 3.456, and at the 1 per cent level this is statistically significant.

RV = weight of right ventricle.
LV = weight of left ventricle.
B = body weight.

## COMMENT

In this experiment the exposure of rats to a high concentration of oxygen at normal barometric pressure produced pulmonary changes which were identical with those described by previous writers as occurring in animals exposed to air at high barometric pressure, with the notable exception of the arterial and arteriolar changes described by Smith and co-workers[3] and by Bennett and Smith.[4] Perivascular fibrosis, which these authors described, did occur but was not striking. Significant medial and intimal changes were not observed.

The study of the ventricular weights of the hearts indicates that a definite right ventricular hypertrophy occurred as early as one week after the beginning of exposure. A less significant right ventricular hypertrophy was present in the animals that died or were killed seven to fifteen months after exposure. The cause of the right ventricular

hypertrophy is not elucidated inasmuch as the effects of the inflammatory pulmonary disease cannot be excluded. As the same inflammatory changes were present in controls, their development was not dependent on the exposure to oxygen. The controls were inadequate for a statistical study of their heart weights.

Unfortunately, satisfactory readings of pulmonary arterial blood pressure were not obtained, so that the study gives no opportunity to determine the correlation between right ventricular hypertrophy and pulmonary hypertension. However, the pulmonary hypertension demonstrated convincingly by Bennett and Smith [4] strongly suggests its correlation with the right ventricular hypertrophy.

## SUMMARY

Fifty young adult rats were exposed to 80 to 85 per cent oxygen at normal barometric pressure for periods ranging from four to twenty-eight days. Animals were studied which died during exposure and which died or were killed at varying intervals after exposure.

The characteristic acute pulmonary changes previously described as "fibrinous pneumonia" were found in animals dead on the fourth day of exposure. These changes were present but less severe in animals dead on the seventh day of exposure and were absent in animals dead on or after the fourteenth day of exposure.

No significant sclerotic changes were found in the pulmonary arteries and arterioles.

Striking bronchitis, bronchopneumonia, bronchiectasis and emphysema were found in the experimental animals and were also present in controls.

Definite right ventricular hypertrophy was demonstrated in animals on which autopsies were made seven to forty-one days after the beginning of exposure and a less significant hypertrophy in animals examined seven to fifteen months after exposure to high oxygen tension. Whether this right ventricular hypertrophy was caused by the exposure to oxygen or by inflammatory pulmonary disease is not clear.

# EFFECT ON THE PROSTATE GLAND OF OCCLUSION OF ITS DUCTS

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AND
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Ligation of the ducts of a secretory gland may or may not produce atrophy of the gland. It is well known that atrophy occurs following ligation of the ducts of the pancreas [1] and of the salivary glands,[2] whereas ligation of the vas deferens [3] does not produce atrophy of the testis.

There is conflicting evidence concerning occlusion of the ducts of the prostate gland. Farrell and Lyman [4] ligated the neck of the bladder and the urethra proximally and distally to the prostate gland in 3 dogs and found atrophy of the prostatic epithelium after five months of obstruction. On the other hand, sections of prostate gland transplanted to the sheath of the rectus abdominis muscle in dogs survive and do not undergo atrophy,[5] and Heckel and Kretschmer [6] and Moore, Rosenblum, Tolins and Melchionna,[7] using rabbits, transplanted prostatic tissue to the anterior chamber of the eye, with functional survival in animals which had physiologically active testis tissue. The results of previous investigations, therefore, are contradictory, although it is conceivable that obstruction in a normal gland with intact secretory nerves is quite different from retention in a closed graft.

The prostate gland undergoes atrophy in the absence of androgen, and it has been pointed out [8] that caging in the laboratory not infre-

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quently causes a depression of the male genital complex in dogs. In the experiments of Farrell and Lyman no measures were undertaken to insure the presence of androgen—e. g. by injecting an androgen.

The problem was of further interest because closely grouped distended cysts are a prominent feature in the spontaneous prostatic hypertrophy of dogs. Accordingly the following experiments were carried out.

## EXPERIMENTS

Six young adult dogs were selected on the following basis, which excluded spontaneous prostatic hypertrophy: The eyes were free from lenticular opacities; erosion and secondary dentin were absent from the teeth; no gross tumors were palpable in the testes, and the prostate on rectal examination was about the size of a small walnut.

With the dog under ether anesthesia and with aseptic precautions, a paramedian incision was made in the left lower quadrant of the abdomen and the prostate gland delivered into the incision; no cysts were palpated or seen in the prostate of any of the dogs. The neck of the bladder was transected just above the prostate, and the neck of the bladder was closed by continuous suture of fine silk; a suprapubic cystostomy was then formed in the dome of the bladder by the insertion of a heavy brass cannula brought out through a stab incision. The circumference and the anteroposterior length of the prostate were measured for comparison with these dimensions at the termination of the experiment. The mucosa of the prostatic urethra was then excised by sharp dissection and cut away as a cuff, the distal portion being sutured with silk. A free graft of fascia and muscle was cut from the sheath of the rectus abdominis muscle and placed in the prostatic bed from which the urethra had been removed, and the proximal part of the prostate was closed over it with silk suture.

The experiments were terminated at nine, ten, forty-five, fifty-three, eighty and one hundred and twenty-eight days. In 2 cases testosterone propionate (Schering) dissolved in sesame oil was injected intramuscularly: in one case 5 mg. for twenty-eight days, and in the other 10 mg. for ten days. An ocular micrometer was used to determine the height of epithelial cells in paraffin sections stained with hematoxylin and eosin.

## RESULTS

The graft survived in all cases and was recognized as a solid patch of entwined connective tissue cells, usually with an adjacent column of fat cells; in 2 dogs a part of the graft had disappeared, while in 4 dogs it seemed to have survived almost completely. In 1 case the urethra reformed along one segment of the graft, displacing the fascia laterally.

In experiment 980, of fifty-three days' duration, in which there was no injection of androgen, the prostatic acini were atrophic and remained as collapsed undistended cords of cells; the graft was clearly recognized and had become closely anastomosed to the adjacent connective tissue of the prostate. In this dog the testes were found atrophic at the end of observation.

In the remaining 5 cases there was marked distention of acini in *areas* of the gland, and groups of adjacent acini were greatly distended. In all of these cases there were areas of normal prostate gland, as well

Fig. 1.—Canine prostate gland forty-five days after excision of the prostatic urethra and replacement by a fascial graft. The connective tissue plug occupies the center of the field; above and to the right are seen distended prostatic acini.

as regions in which the acini were dilated (figs. 1 and 2). In the dogs treated with testosterone propionate the epithelium in the areas of dilatation varied from flat to cuboidal, the tallest cells being 7.5 to 10

microns in height; this epithelium was distinctly lower than in the normal regions of the gland (table). In the untreated animals the epithelium in the regions of dilated acini was mostly flat or occasionally low cuboidal.

These results are in line with the findings in experimental free grafting of prostatic tissue and are opposed to the findings of Farrell

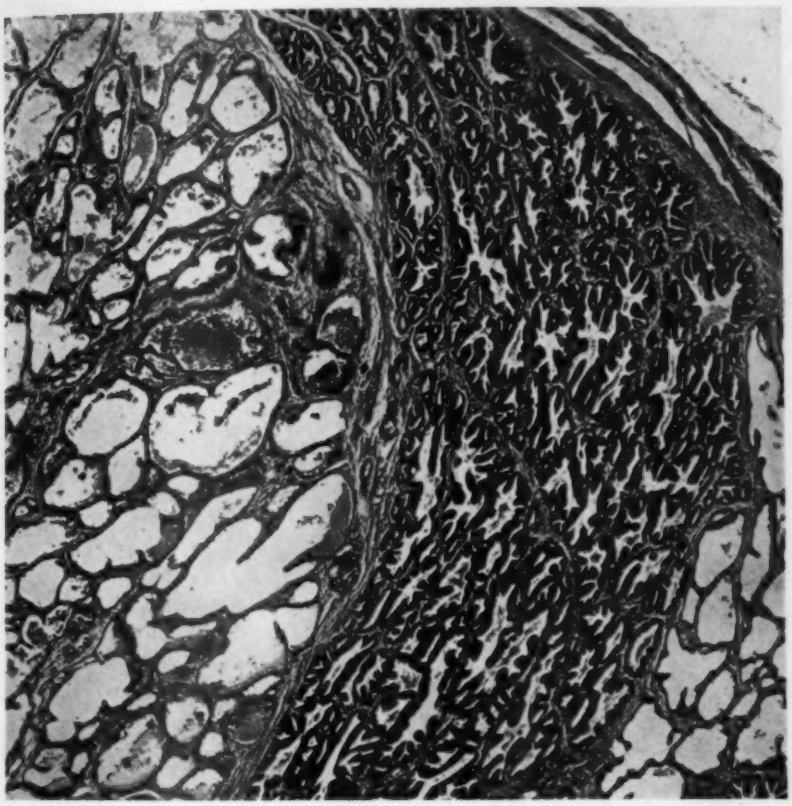

Fig. 2.—Canine prostate gland one hundred and twenty-eight days after excision of the prostatic urethra and replacement by a fascial graft, demonstrating two areas of dilated acini separated by an area of normal prostatic tissue; × 60. This dog was given subcutaneous injections of testosterone propionate, 10 mg. daily for ten days before the termination of the experiment.

and Lyman. In the absence of androgen the prostate gland is atrophic and the acini undistended, while in the presence of androgen the obstructed acini are dilated. In connection with the areas of acinous dilatation, interposed between areas of normal prostatic tissue, it seems

reasonable that only the ducts draining the dilated acini were obstructed, while ducts draining the undilated ones were preserved or were reformed following this operation.

In both canine and human prostate glands (fig. 3) at times areas may be seen closely resembling the areas with duct obstruction found

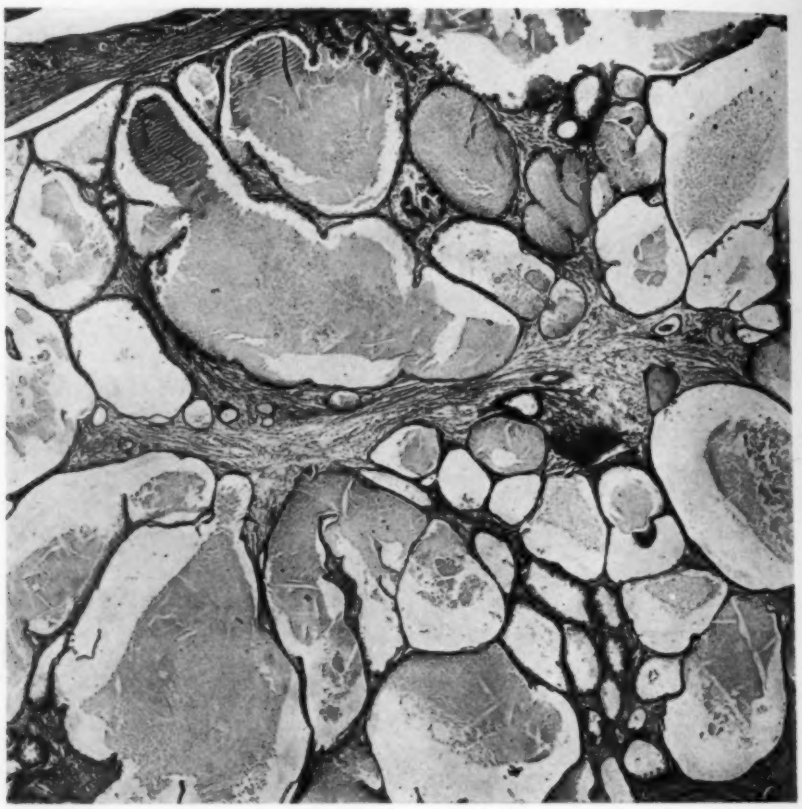

Fig. 3.—Hypertrophy of the human prostate; × 100. Note dilated prostatic acini similar to those found in dogs with obstructed prostatic ducts.

*Measurements of the Prostate Glands in Dogs with Obstructed Prostatic Ducts*

| Experiment | Duration, Days | Testosterone Propionate Injected, Mg. × Days | Original Measurements of Prostate | | Final Measurements of Prostate | | | Height of Prostatic Epithelium in | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Circumference, Cm. | Length, Cm. | Circumference, Cm. | Length, Cm. | Weight, Gm. | Dilated Region, Microns | Normal Region, Microns |
| 881 | 10 | None | 6.7 | 3.1 | 6.9 | 3.2 | 5.9 | 2.5-5 | 5- 7.5 |
| 853 | 45 | 5 mg. × 28 days | 5.3 | 3.0 | 7.5 | 3.5 | 7 | 5-10 | 12.5-17.5 |
| 921 | 128 | 10 mg. × 10 days | 8 | 4.5 | 7.6 | 3.7 | 8.76 | 5-7.5 | 15 -20 |

in this experiment. Judging from similarity of microscopic observations, one may assume that at times complete obstruction of the ducts occurs in these species.

## SUMMARY

Obstruction of prostatic ducts produced by excision of the prostatic urethra and replacement by a free graft of fascia led to regional dilatation of acini, interposed between normal areas of the prostate gland, in 5 dogs in which the obstruction lasted from ten to one hundred and twenty-eight days. In some of these dogs androgens were produced in adequate amounts; in others they were supplied by injection. In 1 dog with obstruction of prostatic ducts there was complete atrophy of the prostatic epithelium, which persisted in the form of undilated islands and cords of cells; this atrophy was related to an insufficiency of circulating androgens.

## CONCLUSIONS

Obstruction of the prostatic ducts in dogs does not lead to atrophy but causes cystic dilatation of prostatic acini drained by these ducts, provided the circulating androgens are adequate to maintain the secondary sex characteristics. Comparable microscopic observations of massive acinous dilatation suggest that complete obstruction of prostatic ducts occurs spontaneously in canine and human species.

# INFLUENCE OF HEPTALDEHYDE ON CARCINOGENIC ACTION OF METHYLCHOLANTHRENE

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Experiments by Strong [1] on the induction of retrogressive changes and liquefaction in spontaneous tumors by heptaldehyde have attracted wide interest. The success of Boyland and Mawson [2] in securing some inhibition of spontaneous tumors with heptaldehyde is encouraging. Several investigators, however, have been unable by the injection or feeding of heptaldehyde to obtain any favorable results with either spontaneous or transplanted tumors.[3] The bisulfite addition compound of heptaldehyde and N-heptaldoxime were found ineffective.[4] Price [3c] did not observe any inhibitory effect on tumor production when heptaldehyde was added to the diet of mice treated with methylcholanthrene.

Nevertheless, the demonstration [5] that heptaldehyde is capable of causing the resorption of actively growing tissue (mouse embryos) prompted an experiment slightly different from that of Price. The heptaldehyde was applied directly to the skin where the carcinogen was acting to insure an active concentration of the aldehyde, for little is known about the absorption of heptaldehyde from the gastrointestinal tract.

## EXPERIMENTS

In a preliminary experiment heptaldehyde and methylcholanthrene were applied on alternate days to the interscapular region of the mice, but ulceration followed where these compounds came in contact with moving parts of the mouse, making continued application over a long period difficult. Consequently the site for experimentation was shifted farther caudad.

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From the Research Department of the Barnard Free Skin and Cancer Hospital.

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Small patches of hair were removed from the backs of mice (New Buffalo) by treatment with sodium sulfide. To the control group (34 mice to be treated with methylcholanthrene alone) and to the experimental group (54 mice to be treated with methylcholanthrene and heptaldehyde) methylcholanthrene (0.6 per cent in benzene) was applied every other day, to the center of the epilated area. On alternate days heptaldehyde [6] was applied to the experimental group so that the entire epilated area was covered. About one third of the epilated area was treated with the carcinogen. In both groups the carcinogen and the heptaldehyde were applied from the smooth tip of a capillary tube by gently rolling the tip of the tube over the hairless area while forcing out liquid carefully by pressure on the dropper bulb. This was done to keep the carcinogen well localized and to spread the heptaldehyde in a thin film over the whole epilated area. After fifty to sixty days of painting, the mice were examined at least once a week for the appearance of papilloma and carcinoma.

## RESULTS

Table 1 shows the results in the control group, in which there were 34 mice when the experiment was started. Four died before the first

TABLE 1.—*Production of Tumors with Methylcholanthrene in Controls*

| Duration of Treatment, Days | Number of Mice with | | | Average Survival Time After Tumor Appeared, Days | Total Number of Mice with Tumors | Percentage with Tumors |
|---|---|---|---|---|---|---|
| | Papilloma | Sarcoma | Carcinoma | | | |
| 60- 70 | 0 | 2 | 3 | 82 | 5 | 16.6 |
| 71- 80 | 0 | 0 | 2 | 88 | 7 | 23.3 |
| 81- 90 | 0 | 2 | 7 | 84 | 16 | 53.3 |
| 91-100 | 0 | 0 | 1 | 90 | 17 | 56.6 |
| 101-110 | 1 | 2 | 10 | 57 | 30 | 100.0 |
| Total | 1 | 6 | 23 | | | |
| Percentage | 3.3 | 20.0 | 76.6 | | | |

tumor appeared and are not included in the table. The first tumor occurred at sixty-four days and was classified as papilloma. Although the tumors of all save one control are classified in the table as sarcoma and carcinoma, all of them except one appeared to originate from papilloma. Since the tumors were allowed to grow during continued painting, the histologic classification is that at the end of the experiment. By ninety days 16, or 53 per cent, of the mice had tumors. By one hundred and ten days all of the 30 mice had tumors. One, or 3.3 per cent, had papilloma; 6, or 20 per cent, spindle cell sarcoma, and 23, or 76.7 per cent, keratinizing and infiltrative squamous cell carcinoma. The survival time after the appearance of the tumors ranged from fifty-seven to ninety days. Usually sarcoma arose beneath papilloma or in an area near papilloma. In one mouse sarcoma arose at the place of application of the hydrocarbon, while papilloma arose in the form of a small tumor about 1½ inches (3.5 cm.) from the epilated

6. This was obtained from Eastman; redistilled weekly and stored at 0-5 C.

area. The tumors were rather slow growing, as is evident from the survival time. The methylcholanthrene was applied continuously for one hundred and fifty to one hundred and sixty days, or until the mice died.

Table 2 shows the incidence of tumors in the control group and in the heptaldehyde-treated group for one hundred and twenty days. Evidently heptaldehyde had a marked inhibitory effect. At eighty-one to ninety days 16, or 53.3 per cent, of the controls had tumors, while there was only 1 mouse, or 2 per cent, in the experimental group with a tumor. By one hundred and one to one hundred and ten days all of the controls had tumors, whereas tumors were present in only 2, or 4 per cent, of the experimental group.

TABLE 2.—*Comparison of the Incidence of Tumors Induced by Methylcholanthrene in the Control Group with That in the Heptaldehyde-Treated Group*

| Duration of Treatment, Days | Control Group | | | Heptaldehyde-Treated Group | | |
|---|---|---|---|---|---|---|
| | Mice Treated | Mice with Tumors | Percentage with Tumors | Mice Treated | Mice with Tumors | Percentage with Tumors |
| 60- 70 | 30 | 5 | 16.6 | 49 | 0 | 0 |
| 71- 80 | 30 | 7 | 23.3 | 49 | 0 | 0 |
| 81- 90 | 30 | 16 | 53.3 | 49 | 1 | 2 |
| 91-100 | 30 | 17 | 56.6 | 49 | 1 | 2 |
| 101-110 | 30 | 30 | 100.0 | 49 | 2 | 4 |
| 111-120 | .. | .. | .... | 49 | 3 | 6 |
| 121-130 | .. | .. | .... | 49 | 3 | 6 |

Percental Distribution of Tumors

| | Papilloma | | Sarcoma | | Carcinoma | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Control group (30 mice) | 1 | 3.3 | 6 | 20.0 | 23 | 76.6 |
| Experimental group (23 mice) | 13 | 56.5 | 7 | 30.4 | 3 | 13.0 |

Table 3 is a compilation of the records as to the inhibitory effect of heptaldehyde on the carcinogenic action of methylcholanthrene when these chemicals were applied for from eighty to ninety days to two hundred days. The second column on the left shows the number of mice in which tumors had not developed over each stated period. At the time indicated the other columns show: the number dying without tumors, the number dying with hyperplasia of the epidermis, the number with papilloma, the number with sarcoma and the number with carcinoma. The second column from the right shows the total number of tumors, and in the last column is indicated the percentage of the tumors, occurring at the given period (relative to the total number of developing tumors after one hundred and ten days). The histologic classification is that when the mice died, although the time in days is representative of the initial appearance of the tumors. Many mice died after one hundred and fifty days of treatment without tumors develop-

ing, as is indicated in the table. At one hundred and sixty days there were still 25, or 50 per cent, of these mice without tumors, while 15, or 30 per cent, had tumors. By two hundred days only 1 mouse survived, and on a basis of 49 mice at one hundred and ten days, at which time the first tumors had appeared, 47 per cent had tumors while 53 per cent did not have them. Of the tumors in the former, 13, or 56.5 per cent, were classified as papilloma, and were very small; 7, or 30.4 per cent, were classified as spindle cell sarcoma, while 3, or 13.0 per cent, were classified as squamous cell carcinoma—the largest of these three measured 5 by 5 mm. in its greatest diameters. The largest tumor classed as carcinoma in the control group measured 24 by 35 mm.

TABLE 3.—*Influence of Heptaldehyde on the Carcinogenic Action of Methylcholanthrene in Experimental Animals*

| Duration of Treatment, Days | Number of Mice | | | | | | Average Survival Time After Tumor Appeared | Total No. of Tumors | Percentage of Tumors* |
|---|---|---|---|---|---|---|---|---|---|
| | Without Tumors | Died Without Tumors | Died with Hyperplasia | With Papilloma | With Sarcoma | With Carcinoma | | | |
| 80- 90..... | 48 | 0 | 0 | 0 | 1 | 0 | 55 | 1 | 2.0 |
| 91-100..... | 48 | 0 | 0 | 0 | 0 | 0 | .. | 1 | 2.0 |
| 101-110..... | 47 | 0 | 0 | 0 | 0 | 1 | 41 | 2 | 4.0 |
| 111-120..... | 46 | 0 | 0 | 1 | 0 | 0 | .. | 3 | 6.0 |
| 121-130..... | 45 | 0 | 1 | 0 | 0 | 0 | .. | 3 | 6.0 |
| 131-140..... | 39 | 1 | 1 | 2 | 2 | 0 | 23 | 7 | 16.3 |
| 141-150..... | 26 | 4 | 1 | 3 | 3 | 0 | 23 | 13 | 26.5 |
| 151-160..... | 25 | 1 | 0 | 1 | 0 | 1 | 22 | 15 | 30.6 |
| 161-170..... | 18 | 5 | 1 | 1 | 0 | 0 | 17 | 16 | 32.6 |
| 171-180..... | 8 | 4 | 1 | 4 | 0 | 1 | 10 | 21 | 42.8 |
| 181-190..... | 4 | 3 | 1 | 1 | 0 | 0 | 6 | 22 | 45.0 |
| 191-200..... | 1 | 0 | 2 | 0 | 0 | 0 | .. | 22 | 45.0 |
| 220-230..... | 0 | 0 | 0 | 0 | 1 | 0 | .. | 23 | 47.0 |
| Total..... | | 18 | 8 | 13 | 7 | 3 | | | |
| Percentage | | 36.7 | 16.3 | 26.5 | 12.2 | 6.1 | | | |

* Relative to total number of developing tumors after one hundred and ten days.

From the standpoint of inhibition not only is the number of mice in which tumors did not develop and the number with small tumors of the papilloma type significant, but the small size of the tumors, except those classed as sarcoma, compared with the controls, is also remarkable. The extent of inhibition is also shown when the distribution of the tumors in the control and experimental groups is examined (table 2). The control group had only 1 tumor (3.3 per cent) classifield as papilloma, while the experimental group had 13, or 56.5 per cent. In the control group 76.6 per cent, and in the aldehyde-treated group 13.0 per cent, of the tumors were carcinoma. This marked difference in the proportions of papilloma and carcinoma is indeed obviously evidence of the inhibitory effect of heptaldehyde, not only in lowering the number of mice in which tumors develop but in lessening

the malignant transformation of these tumors. Apparently heptaldehyde has much less influence on sarcoma because the protected sites of growth of this type of tumor prevent much absorption of the aldehyde. As the painting time increases, the survival time decreases. Perhaps the long-continued application of benzene is not well tolerated by the mice.

Fig. 1.—The treatment of mouse skin with methylcholanthrene and heptaldehyde produced a moderate degree of hyperkeratosis, atrophy of the epidermis and infiltration of the dermis by monocytes, plasma cells and mast cells. Bouin fixation and hematoxylin and eosin stain; × 132.

To ascertain the influence of heptaldehyde on papilloma and carcinoma induced by methylcholanthrene in the control group, 5 males and 3 females, which had small to large tumors classified as papilloma (4 mice) or small tumors classified as carcinoma (4 mice) were treated as follows: Freshly distilled heptaldehyde was applied with a medicine dropper over the surface of the entire tumor once a day, and each tumor

was measured (maximum diameter) every five days. Although the treatment was continued for thirty-five days, there was no effect on the growth of these tumors. During the aldehyde treatment the carcinogen was not applied. This failure of heptaldehyde to influence these tumors might be expected, since some of the experimental mice showed tumors when the aldehyde was applied every other day.

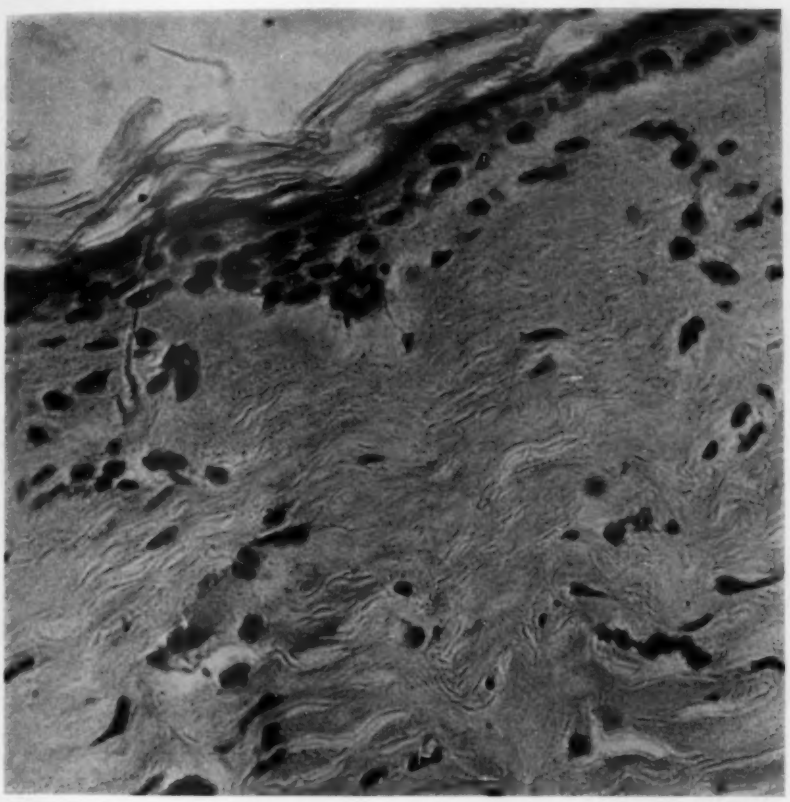

Fig. 2.—Section of skin showing extensive fibrosis present in the tissue resistant to the development of tumors when both methylcholanthrene and heptaldehyde were applied. Bouin fixation and hematoxylin and eosin stain; × 132.

The following changes were observed in the skin of the heptaldehyde-treated group of mice in which tumors did not develop. Grossly the skin appeared atrophic with loss of hair. Microscopically, marked atrophy of the epidermis, a moderate degree of hyperkeratosis, keratin plugging of the hair follicles and extensive fibrosis of the dermis (figs. 1 and 2) were seen. The cells in the epidermis showed keratinization of the cytoplasm, and the nuclei were small and pyknotic. Infiltration

of the dermis by monocytes, plasma cells and mast cells was noted. The larger blood vessels showed perivascular mononuclear infiltration. Rarely was necrosis of the epidermis present with ulcer formation. The general picture resembled the fibrosis of skin following radiation therapy.

## COMMENT

Orr and Strichland [3c] found that saturation of the Ringer bicarbonate medium with heptaldehyde completely abolished all glycolytic activity of both tumor and normal tissues. Crabtree [7] observed that substances which check the utilization of dextrose by tissues cause a delay in the appearance of warts induced by 3,4-benzpyrene or by 1,2,5,6-dibenzanthracene. The amount of delay was exactly parallel to the reactivity of the chlorine atoms of the substance tested in the case of chlorine compounds known to possess definite degrees of chemical reactivity. This led to the inference that an inhibition of the glycolytic processes in the epithelial cells of mice might result in a corresponding inhibition of the processes concerned in the induction of tumors by carcinogenic hydrocarbons. On increased concentration of these substances, however, the inhibitory effect was no longer present. In some cases stimulation was noted. Crabtree concluded that the biochemical property of inhibiting cell glycolysis can, under different experimental conditions, either retard or accelerate the rate of production of tumors by carcinogenic hydrocarbons.

Berenblum and co-workers [8] demonstrated that $\beta\,\beta'$-dichlorodiethylsulfide, $\beta\,\beta'$-dichlorodiethylsulfone and cantharidine, which are anticarcinogenic to the action of tar, reduce the glycolysis of minced Jensen sarcoma tissue in vitro more than they do the respiration of this tissue. But compounds such as $\beta\,\beta'$-dichlorodiethylsulfoxide, thiodiglycol and croton oil, which are not anticarcinogenic, do not decrease glycolysis more than respiration. Ethylene-bis-$\beta$-chloroethylsulphide has no selective action on glycolysis, although it inhibits the induction of tumors.

The work of Orr and Strichland suggests that the inhibitory effect of heptaldehyde on the carcinogenic action of methylcholanthrene may be due to its inhibitory effect on the glycolytic activity of epithelial cells, which would take place to a lesser degree when the drug was added to the food in the experiments of Price. There is also the possibility that heptaldehyde may partially inactivate or combine with methylcholanthrene to lessen its carcinogenic potency. Experiments are in progress

7. Crabtree, H. G., in Thirty-Seventh Annual Report, 1938-1939, of the Imperial Cancer Research Fund, London, 1939, p. 9.

8. Berenblum, I.; Kendal, L. P., and Orr, J. W.: Biochem. J. **30**:709, 1936.

to test this idea. Hoffman and associates [9] have suggested the possibility that the anticarcinogenic influence of heptaldehyde reported by Strong may be due to the conversion of this chemical to heptylic acid by the tissues. Attempts are being made to enhance the inhibitory effect of heptaldehyde by the addition of antioxidants which may prolong its action on the skin.

SUMMARY

Heptaldehyde is capable of markedly inhibiting the carcinogenic action of methylcholanthrene when the skin of the backs of mice is painted with it on alternate days with methylcholanthrene. The proportion of papilloma and of carcinoma in the control group, painted with methylcholanthrene alone, compared with that in the heptaldehyde-treated group, is further evidence of the inhibitory effect, since the number of tumors classed as carcinoma in the experimental group was small, while in the control group it was large. The ratio of papilloma was just the reverse. Possible explanations for this inhibitory effect are offered. Heptaldehyde had no effect on papilloma and carcinoma once they had started to grow (in the control group).

9. Hoffman, C.; Schweitzer, T. P., and Dalby, G.: Am. J. Cancer **38**:569, 1940.

# EFFECTS OF YELLOW PHOSPHORUS AND ARSENIC TRIOXIDE ON GROWING BONES AND GROWING TEETH

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CHICAGO

The purpose of this investigation was to study and compare the effects of prolonged administration of yellow phosphorus on growing bones and growing teeth and to determine, if possible, the mechanisms of these effects.

Wegner,[1] in 1872, was the first to produce experimentally transverse bands of increased density in the metaphysial regions of growing long bones by feeding yellow phosphorus over prolonged periods. We have chosen to designate these bone changes as *phosphorus bands*. Phemister,[2] in 1918, was the first to describe the roentgenographic appearance of phosphorus bands. One of us (C. O. A.) reported[3] that yellow phosphorus has no appreciable effect on the healing of fractures in rabbits and that no increased density was found in the callus about the fracture site, although definite phosphorus bands were present in the metaphyses of the same bone. Chemical studies of the bone laid down during the administration of yellow phosphorus have been reported to give normal results.[4] Compere[5] reviewed the literature concerning the effects of ingestion of yellow phosphorus on bone. No reports on the effects of yellow phosphorus on growing teeth have been found.

## METHOD AND MATERIAL

Seven litters totaling 34 rabbits from 27 to 87 days of age and five litters totaling 32 rats from 28 to 56 days of age were used. The rabbits received a stock diet. The rats received a diet described by Goisman and Compere.[6] The minimal dose of yellow phosphorus necessary to produce characteristic increased metaphysial density in growing long bones was used. No study of the effects of large doses of yellow phosphorus was made.

From the Division of Orthopaedics, Department of Surgery, University of Chicago (Dr. Adams) and the Department of Histology, College of Dentistry, University of Illinois (Dr. Sarnat).

1. Wegner, G.: Virchows Arch. f. path. Anat. **55**:11, 1872; **61**:44, 1874.
2. Phemister, D. B.: J. A. M. A. **70**:1737, 1918.
3. Adams, C. O.: Proc. Soc. Exper. Biol. & Med. **38**:449, 1938.
4. Adams, C. O.: Proc. Soc. Exper. Biol. & Med. **39**:351, 1938.
5. Compere, E. L.: Am. J. Dis. Child. **40**:941 and 1177, 1930.
6. Goisman, J., and Compere, E. L.: J. Bone & Joint Surg. **20**:587, 1938.

About one half of the rabbits were given daily a 0.6 mg. coated pill of yellow phosphorus for periods varying from thirteen to one hundred and seventeen days. The pill was thrust into the throat with a curved hemostat, so that the animal was forced to swallow it. Two rabbits were given in a similar manner a 0.6 mg. tablet of arsenic trioxide daily for twenty-eight days. The daily dose was gradually increased to 6.0 mg. Equal numbers of litter mates were used as controls.

Yellow phosphorus was given to 14 rats for periods varying from twenty-two to fifty-seven days by replacing the cod liver oil of the diet with standard phosphorized cod liver oil. This contains 0.01 per cent yellow phosphorus. In the diets of 6 of these rats the yellow phosphorus was increased fourfold during the last weeks of the experiment. Arsenic trioxide was administered to 5 rats by mixing the powdered drug with the dry diet. The dose, which was increased each week, varied from 0.002 to 0.05 per cent. Equal numbers of litter mates were used as controls.

Fig. 1.—Roentgenograms of tibias of 4 litter mate rats. The experiment lasted from the thirty-fifth to the sixty-third day of life. Rat 91 was a normal control. Rat 94 had yellow phosphorus (0.01 per cent) added to the cod liver oil of its diet from the thirty-fifth to the forty-ninth day, and rat 95, from the thirty-fifth to the sixty-third day. Rat 97 received a diet containing 0.006 per cent arsenic trioxide during the first week, 0.012 per cent during the second week, 0.025 per cent during the third week and 0.050 per cent during the fourth week. In the metaphyses (*M*) of rats 94 and 95 the increased density corresponding to the period during which yellow phosphorus was administered is readily evident. The increased width of the metaphyses (*M*) due to the diminution of the tubulation process caused by the yellow phosphorus is seen in the tibias of rats 94 and 95. No difference is seen between the tibias of rats 91 and 97, the normal and the arsenic-fed animal.

The animals were weighed at the beginning and at the end of the experiments. Roentgenograms of the tibias were taken at the beginning, at intervals during the experiments and just before death. Roentgenograms were also made of the cleaned tibias, split heads and ground sections of incisor teeth. Measurements of

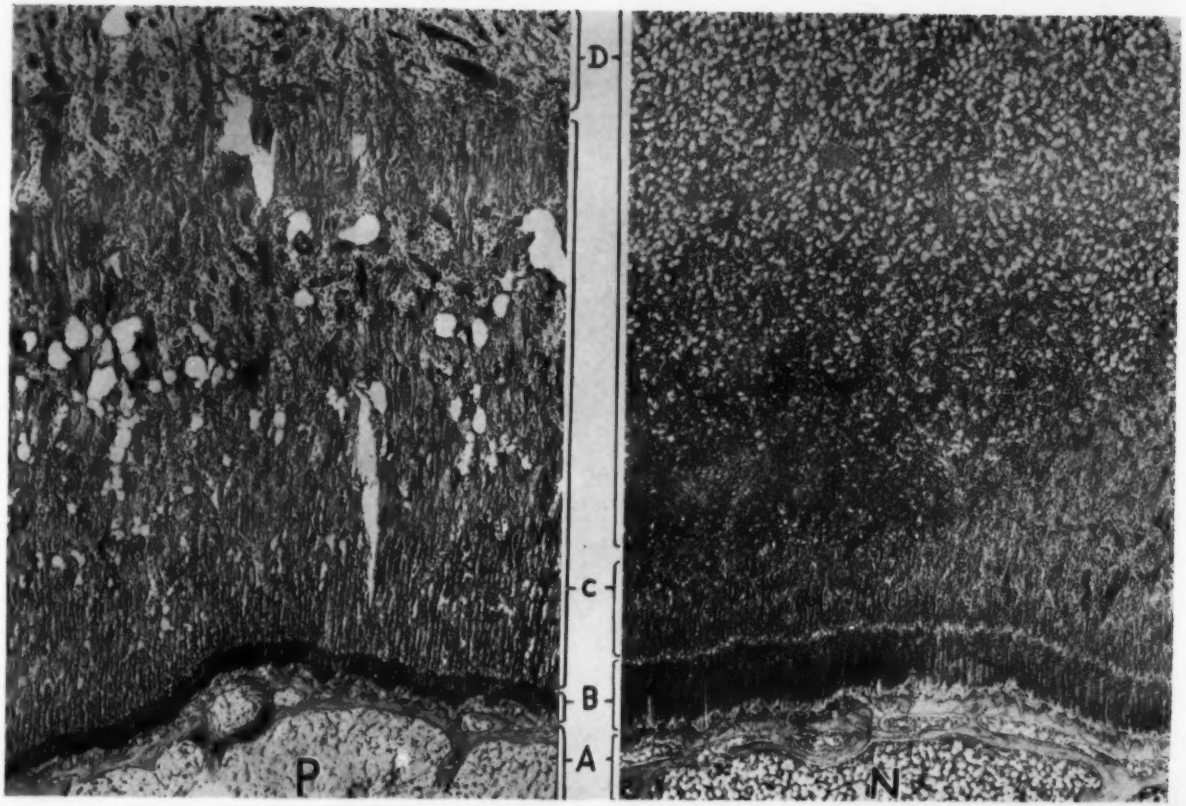


Fig. 2.—Photomicrographs of sections from proximal tibial metaphyses of a rabbit (*P*) which received 0.6 mg. of yellow phosphorus daily for twenty-six days and its control litter mate (*N*); hematoxylin and eosin; × 35. *A* indicates the normal spongy bone of the epiphysis; *B*, the epiphysial plate, which is narrower in animal *P*; *C*, the zone of metaphysial trabeculae, which are increased in number and extend much farther into the diaphysis in animal *P*; *D*, the diaphysial marrow, which is less cellular in animal *P*. The changes in *P* are more marked than the average for animals which are given yellow phosphorus.

the tibial diaphyses were made from these roentgenograms and the amount of growth calculated. Sections of the proximal thirds of the tibias and of the incisor and molar teeth were prepared and stained with hematoxylin and eosin.

## RESULTS

*Growing Long Bones.*—The animals which received yellow phosphorus failed to gain as much weight as did the controls. There was considerable variation in the longitudinal growth of the tibias in the various animals. However, the average daily growth of the tibial diaphysis was 0.27 mm. in the rabbits receiving yellow phosphorus, while it was 0.36 mm. in the control litter mates.

The phosphorus bands in the proximal end of the tibia corresponded to the periods during which the animal received yellow phosphorus (figs. 1 and 3). In some of the animals which received yellow phos-

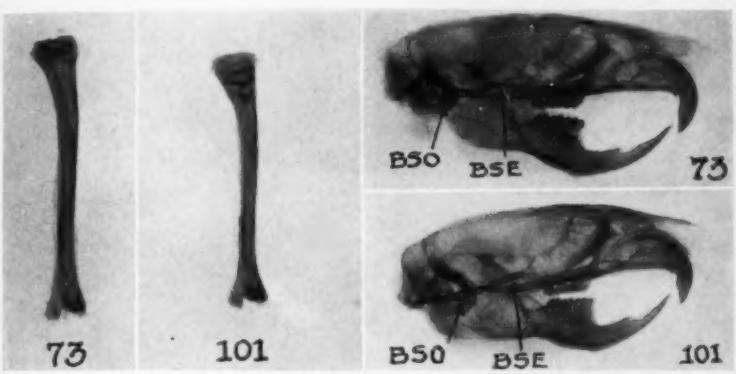


Fig. 3.—Roentgenograms of tibias and midsagitally sectioned skulls of rat 73, normal, and rat 101, which had 0.01 per cent yellow phosphorus added to the cod liver oil of its diet in the first, third and fifth weeks of the experiment. Both animals were killed at the end of the sixth week of the experiment. Three dense metaphysial bands corresponding to the periods of ingestion of yellow phosphorus are present in the proximal end of the tibia of animal 101. An increased density is seen on both sides of the basispheno-occipital (*BSO*) and basisphenopresphenoid (*BSE*) junctions. No changes are noted in the incisor or molar teeth of animal 101.

phorus over a period of four or more weeks there was definite retardation in the normal process of tubulation (fig. 1).

In the microscopic section the epiphysial cartilage plate is usually narrower in the animal given yellow phosphorus (fig. 2). The number of cartilage cells in each column is reduced, particularly that of the immature cells near the epiphysial side of the plate. The metaphysial zone of increased density seen in the roentgenograms (fig. 3) of the animals which received yellow phosphorus is readily evident in the histologic sections (fig. 4 *A*). In such zones (fig. 2) there are many more trabeculae than normal. These trabeculae contain more than the

animal *P*; *D*, the diaphysial marrow, which is less cellular in animal *P*. The changes in *P* are more marked than the average for animals which are given yellow phosphorus.

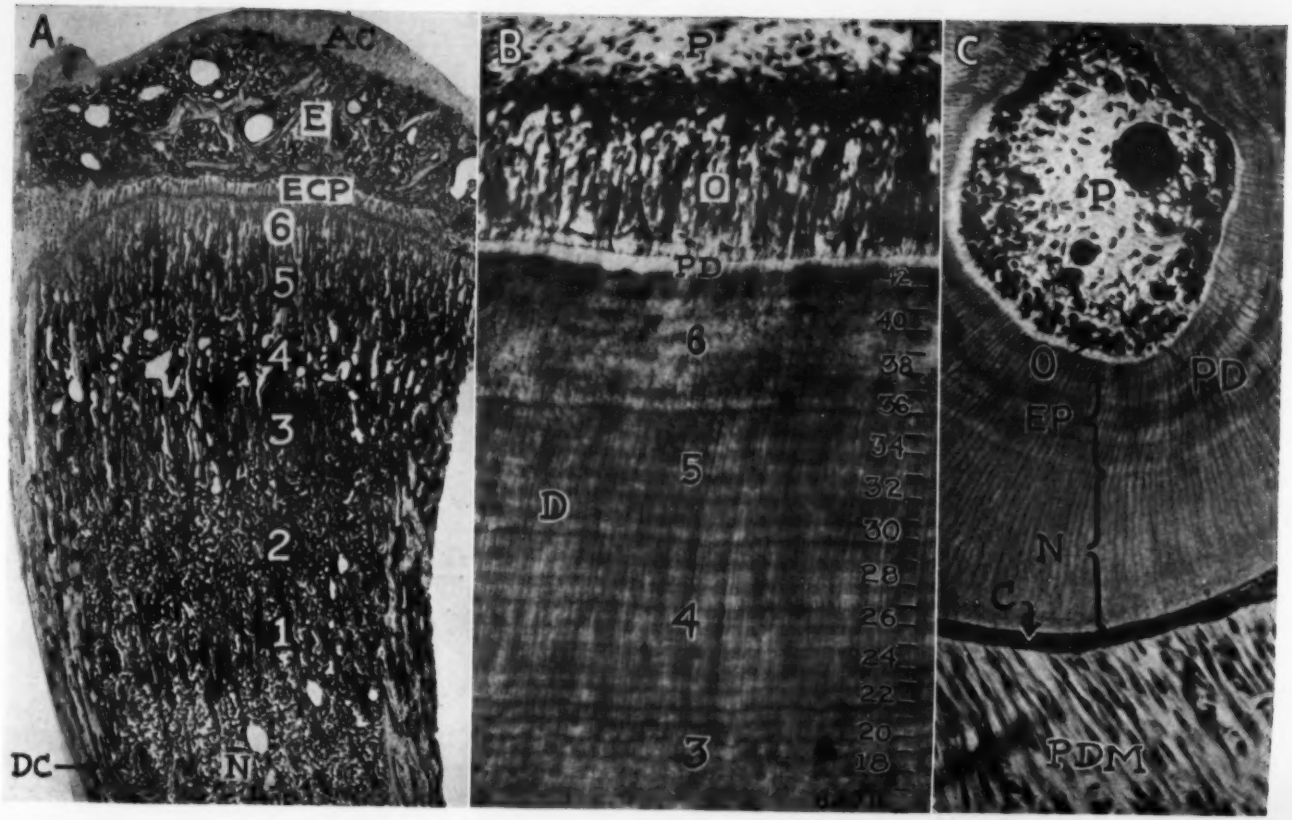


**Figure 4**

*(See legend on opposite page)*

normal amount of calcified cartilage matrix. They are also present abnormally far in the diaphysis. These changes vary with the duration of the administration of yellow phosphorus. The new bone laid down in the formation of the trabeculae appears normal. In several animals which received yellow phosphorus the hemopoietic marrow is partially replaced by loose fibrous tissue.

The animals fed arsenic trioxide showed more nearly normal weight and tibial growth than the animals fed yellow phosphorus. However, no definite roentgenographic or histologic changes have been found in the tibias of these animals.

*Growing Teeth.*—No roentgenographic changes are found in the teeth of the animals receiving yellow phosphorus (fig. 3). In the roentgenograms of the skulls, however, it is noted that there is a phosphorus band on both sides of the basispheno-occipital and basisphenopresphenoid junctions. Growth of these basal skull bones is by endochondral ossification, whereas most of the remaining skull bones grow by membranous ossification. The latter bones appear to be unaffected by the administration of yellow phosphorus.

The histologic sections of the incisors and molars of the rats receiving either yellow phosphorus (figs. 4 *B* and *C*) or arsenic trioxide (fig. 5 *B*) show zones of disturbed calcification in the dentin. In the incisal dentin the incremental pattern is accentuated. These zones correspond closely with the periods when the drug was administered as calculated by the incremental pattern and the rate of apposition of the dentin of the rat incisor [7] and molar.[8] The alteration of the diet is reflected in the incisal dentin by a deeply hematoxylin-stained narrow stripe (fig. 5 *A*).

7. Schour, I., and Hoffman, M. M.: J. Dent. Research **16**:349, 1937.
8. Hoffman, M. M., and Schour, I.: J. Dent. Research **17**:307, 1938.

LEGEND FOR FIGURE 4

Fig. 4.—Photomicrographs of hematoxylin and eosin stained sections of (*A*) the proximal end of a tibia (× 20), (*B*) the labial dentin of an incisor tooth (× 221) and (*C*) a molar tooth (× 315) of rat 101, which received an addition of 0.01 per cent yellow phosphorus to the cod liver oil of the diet during the first, third and fifth weeks of the experiment and was killed at the end of the sixth week. In *A*: *AC*, articular cartilage; *E*, epiphysis; *ECP*, epiphysial cartilage plate; *DC*, diaphysial cortex; *N*, preexperimental period. In *A* and *B*: *1*, *3* and *5*, the effects of yellow phosphorus administered during the first, third and fifth weeks; *2*, *4* and *6*, the periods of the second, fourth and sixth weeks, during which no yellow phosphorus was administered. In *B*: *D*, dentin. In *B* and *C*: *P*, pulp; *O*, odontoblasts; *PD*, predentin. In *C*: *PDM*, periodontal membrane; *C*, cementum; *N*, preexperimental period; *EP*, the experimental period. Because the rat incisor (*B*) is a tooth of continuous growth and eruption, the record of only the last four weeks remains. The rat molar (*C*), which is a tooth of limited growth and eruption, will retain the record permanently. The rate of apposition of dentin of the rat molar is much less than that in the incisor.

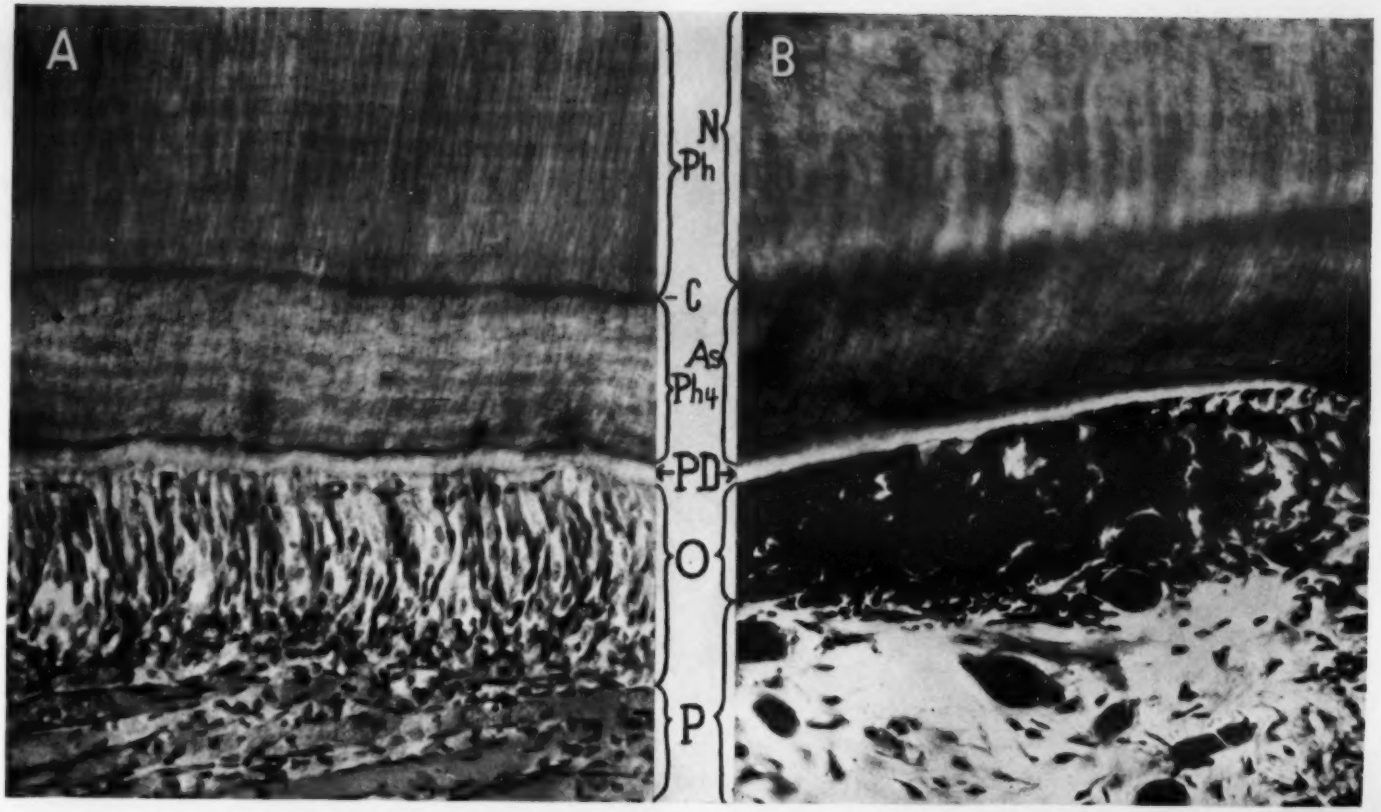


Fig. 5.—*A*, photomicrograph (× 277) of a hematoxylin and eosin stained section of the labial dentin of an incisor of rat 42; *Ph*, the period during which 0.01 per cent yellow phosphorus was added to the cod liver oil of the diet; $Ph_4$, the period during which the yellow phosphorus was increased to 0.04 per cent; *C*, the "calciotraumatic line"; *PD*, predentin; *O*, odontoblasts; *P*, pulp.

*B*, photomicrograph (× 560) of a hematoxylin and eosin stained section of the molar dentin of rat 97; *N*, the period of normal diet; *As*, the period during which arsenic trioxide (0.006 to 0.050 per cent) was present in the diet; *PD*, predentin; *O*, odontoblasts; *P*, pulp.

Any increase in the dose of either yellow phosphorus or arsenic trioxide produced in the dentin of the incisor a separate zone of more disturbed calcification distinct from the zone caused by the smaller dose (fig. 5*A*). Changes in the calcification of the dentin caused by arsenic trioxide and yellow phosphorus cannot be distinguished.

## COMMENT

*Growing Bone.*—Yellow phosphorus in the dosages stated has a general effect on the animal, as evidenced by failure to gain weight normally and retardation of longitudinal bone growth. The reduction in the rate of growth of the long bones may be the direct effect of the drug on the epiphysial cartilages. It is more likely, however, that both of these effects are due to the general toxic action of yellow phosphorus, as a similar diminution in weight gain and long bone growth was produced by arsenic trioxide.

Microscopic study shows that the increase in the number of trabeculae is apparently due to a reduced resorption of the intercellular calcified cartilage matrix which is left when the cartilage cells are released and disappear on the diaphysial side of the epiphysial cartilage plate. Normally, a large percentage of this matrix is resorbed, leaving only a few spicules on which bone is deposited. Yellow phosphorus evidently reduces this resorption and leaves many more spicules of matrix on which new bone is laid down. There results a great increase in the number of trabeculae in the metaphysis. Resorption of these newly formed trabeculae occurs less readily than normal, as evidenced by the retardation of tubulation and by the abnormal persistence of these trabeculae in the diaphysis. The process of tubulation is dependent on peripheral and central resorption of metaphysial bone. Additional new bone is deposited only in the portion destined to become the cortex of the shaft. The trabeculae in the metaphyses of the animals fed yellow phosphorus persist longer than normal. If resorption were not decreased, these trabeculae would extend into the diaphysis a lesser distance than normal, as the longitudinal growth is retarded simultaneously. The increase in number and length of trabeculae and the decrease in resorption of these account for the increased amount of bone in this region and for the transverse metaphysial bands of increased density seen in the roentgenograms. Kassowitz,[9] in 1884, was the first to suggest that this effect of yellow phosphorus was due to decreased resorption of bone and cartilage matrix.

This diminution of bone resorption is probably generalized, but only in the metaphyses, where resorption is normally very active, is it readily evident. This explains why the dense bone resulting from the administration of yellow phosphorus is readily demonstrable only in the complicated process of endochondral ossification. In the physiologic

9. Kassowitz, M.: Ztschr. f. klin. Med. **7**:36, 1884.

processes in which bone production is not accompanied by equally active bone resorption, as in membranous bone formation and healing fractures, yellow phosphorus produces no readily evident change. Wegner [1] reported that prolonged administration of yellow phosphorus causes the normally hollow long bones of chickens to become almost solid masses of dense bone. This is evidence of the generalized reduction of bone resorption.

*Other Causes of Metaphysial Bands.*—Metaphysial bands of increased density in growing long bones are nonspecific as to cause. Lines resulting from arrest of growth in acute illnesses are one type.[10] Gies,[11] in 1877, reported that arsenic trioxide if given in increasing doses produces metaphysial bands of increased density in growing dogs. We were not successful, however, in producing bands in the rabbit or the rat with this substance. Bismuth has been reported by Caffey [12] as a cause of metaphysial bands in children, and he produced bismuth bands in puppies. It is well known that lead produces lead bands in the metaphyses of growing children. It is believed by some that lead produces this increased metaphysial density because of actual deposition of the element in the newly formed bone. Caffey [13] produced metaphysial bands of increased density by feeding lead acetate to dogs. He found by chemical analysis that the bone dissected from the lead-produced bands in the metaphyses contained only 0.7 mg. of lead per gram of dry bone. He reported also that lead did not produce metaphysial changes in growing rabbits and guinea pigs. We attempted to produce lead bands in the bones of growing rats, using diets which varied from 0.00001 to 1.0 per cent of lead acetate. No roentgenographic or histologic changes were found. The histologic appearance of a lead band as shown and described by Park, Jackson and Kajdi [14] and also by Caffey [13] is not dissimilar from that of a phosphorus band. For these reasons, the presence of lead in the dense metaphysial bone is probably only a minor factor in producing the lead band in the roentgenogram, as was suggested by Caffey.

The histologic appearance of the bismuth band in the metaphysis of the dog as described and illustrated by Caffey [12] is also not dissimilar from that of the phosphorus band. It is therefore probable that all types of metaphysial bands and lines of increased density resulting from various factors are produced in the same manner; i. e., by diminution of the resorption of bone and cartilage matrix. It is probable, however, that yellow phosphorus produces these changes more readily than any of the substances yet studied.

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10. Harris, H. A.: Arch. Int. Med. **38**:785, 1926.
11. Gies, T.: Arch. f. exper. Path. u. Pharmakol. **8**:175, 1877.
12. Caffey, J.: Am. J. Dis. Child. **53**:56, 1937.
13. Caffey, J.: Radiology **17**:957, 1931.
14. Park, E. A.; Jackson, D., and Kajdi, L.: Am. J. Dis. Child. **41**:485, 1931.

*Growing Tooth.*—In the rat the incisor grows and erupts continuously, whereas the molar is of limited growth and eruption. For this reason the dentin of the incisor is renewed approximately every thirty-five days, but that of the molar is permanent. The dentin is laid down from the pulpal surface, one layer within the other, and, as Erdheim [15] stated, it is like a kymographic record. Once dentin is formed and calcified, it is, unlike bone, not subject to mineral exchange.[16] The record will last for the life of the dentin. Differences between dentin and bone are stated in the table. Changes in the general condition of an animal may cause abnormal formation and calcification of dentin, which is demonstrable histologically.[16a] Yellow phosphorus and arsenic trioxide have a general deleterious effect on the animal, and consequently the calcification of the dentin produced while the animal is

*Differences Between Endochondral Bone and Dentin*

| Endochondral Bone | Dentin |
|---|---|
| **Normal** | |
| 1. Subject to resorption (record not permanent) | 1. Not subject to resorption (record permanent) |
| 2. Bone preformed in cartilage | 2. Single process of formation and calcification |
| 3. Cellular | 3. Acellular |
| 4. Vascular | 4. Avascular |
| **Affected by Administration of Yellow Phosphorus** | |
| 1. Specific effect (resorption of bone diminished) | 1. Nonspecific effect (no resorption possible, but calcification disturbed) |
| 2. Evident roentgenographically | 2. Not evident roentgenographically |
| 3. Variation in dosage not readily recognizable histologically | 3. Variation in dosage recognizable histologically |

receiving the drug is abnormal. The deeply hematoxylin-stained narrow stripe in the dentin which corresponds to the time of dietary change has been observed also after parathyroidectomy, after hypophysectomy and in fluorosis. This has been termed "the calciotraumatic line" [17] (fig. 5 *A*).

The effect of yellow phosphorus on growing bones is dependent on diminished resorption of bone and cartilage matrix. A similar change in the tooth is not expected because dentin resorption is not physiologic. Comparison of our findings in teeth and bones shows that yellow phosphorus and arsenic trioxide have similar effects in teeth and dissimilar effects in bones. It can be concluded, therefore, that yellow phosphorus has a nonspecific effect on dentin. Since the

15. Erdheim, J.: Frankfurt. Ztschr. f. Path. **7**:295, 1911.

16. (*a*) Schour, I.: Experimental Dental Histophysiology, in Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938. (*b*) Albright, F.; Aub, J. C., and Bauer, W.: J. A. M. A. **102**:1276, 1934. (*c*) Sarnat, B.: Proc. Inst. Med. Chicago **13**:114, 1940.

17. Schour, I.; Chandler, S. B., and Tweedy, W. R.: Am. J. Path. **13**:945, 1937.

rate of long bone growth is diminished, one might also expect the rate of dentin apposition to be diminished. This could be studied by injecting sodium alizarine sulfonate (alizarine red S) and examining ground sections of the growing teeth.[18] By means of the phosphorus bands the rate of growth in long bones has been studied roentgenographically.[19] From our observations, similar studies on roentgenograms of growing teeth would not be possible.

## SUMMARY

The minimal effective doses of both yellow phosphorus and arsenic trioxide have similar general toxic effects on growing rats and rabbits, as evidenced by a reduction in the weight gain and in the growth of the tibial diaphysis.

In the case of the animal given yellow phosphorus, a roentgenogram of the metaphysis of any growing long bone shows a zone of increased density—the *phosphorus band*. This same band can be seen grossly in the split specimen and histologically. There is a reduction in the process of tubulation of the shaft. *These effects are due to diminished resorption of cartilage matrix and bone.* This diminished resorption of bone is probably generalized but is readily evident only in the metaphyses, where extremely active bone resorption is a prominent feature of the process of normal endochondral bone growth.

No similar effect of arsenic trioxide on bone is found in the rat or the rabbit.

In growing incisor and molar teeth of animals given yellow phosphorus and arsenic trioxide, zones of abnormally calcified dentin are found which correspond closely to the periods of ingestion of the drug. This effect is apparently nonspecific.

Disturbances of dentin calcification in the incisors vary with the dosages of yellow phosphorus and arsenic trioxide. No similar variations are observed in the growing long bones.

Zones of increased density corresponding to the periods of ingestion of yellow phosphorus as seen in roentgenograms of growing long bones are not found in roentgenograms of whole and ground sections of the teeth.

Yellow phosphorus can be utilized in roentgenographic studies of bone growth but not in roentgenographic studies of tooth growth.

Yellow phosphorus has a specific effect on growing long bones and a nonspecific effect on the dentin of growing teeth.

Metaphysial bands of increased density caused by acute illnesses, lead, arsenic, bismuth and other substances are probably produced by the same change as phosphorus bands, i. e., by diminution of the resorption of bone and cartilage matrix.

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18. Schour and Hoffman.[7] Hoffman and Schour.[8]

19. Compere, E. L., and Adams, C. O.: J. Bone & Joint Surg. **19**:922, 1937.

# DIPLOMYELIA (DUPLICATION OF THE SPINAL CORD)

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Diplomyelia is a congenital malformation characterized by more or less perfect duplication of the spinal cord involving varying numbers of segments. The lesion is designated by a variety of names, including "doubling," "duplication," "reduplication" and "bifurcation" of the spinal cord and "diastometamyelia." The latter term has rather common usage and in the strict sense refers to any fissuring of the spinal cord regardless of cause, extent and internal appearance of the cord. Consequently, if the latter term is used in reference to the lesion under discussion, the proper designation would be "congenital diastometamyelia with diplomyelia."

In order to obtain a comprehensive understanding of the pathologic and clinical features of this abnormality, we have studied several reviews of the subject, including those of Bruce, McDonald and Pirie [1] (1906), Zalewska-Ploska [2] (1913), Weil and Matthews [3] (1935) and Hamby [4] (1936), as well as a series of case reports. In these articles more than 42 cases are claimed to be instances of true diplomyelia, but some are in reality instances only of artefacts, as shown by Van Gieson [5] and by several of the reviewers mentioned. In this paper we have selected for study 42 cases that seem to be authentic instances of diplomyelia. These might serve as a cross section, at least, of cases observed through the years, and certain pertinent facts concerning them as well as our case are listed in the accompanying table.

The lesion is equally distributed between the sexes and is found at ages varying from fetal life to 76 years. In about one quarter of the cases the lesion was discovered during adolescence or adult life.

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From the Neurological Unit and the Mallory Institute of Pathology, Boston City Hospital.

1. Bruce, A.; McDonald, S., and Pirie, J. H. H.: Rev. Neurol. & Psychiat. **4**:6, 1906.
2. Zalewska-Ploska, C.: Beitr. z. path. Anat. u. z. allg. Path. **55**:417, 1913.
3. Weil, A., and Matthews, W. B.: Arch. Path. **20**:882, 1935.
4. Hamby, W. B.: Arch. Path. **21**:831, 1936.
5. Van Gieson, I.: New York M. J. **56**:336, 1892.

*Data on Forty-Three Cases of Diplomyelia Reported in the Literature*

| Case * | Author | Age | Sex | Level of Doubling | Spina Bifida | Meningocele or Meningomyelocele | Osseous or Osseochondromatous Process | Comment |
|---|---|---|---|---|---|---|---|---|
| 1 | Altman..... | 48 | M | 7th dorsal, lumbar, sacral | 0 | 0 | 0 | |
| 2 | von Ammon..... | .. | .. | Cervical and upper dorsal | + | 0 | 0 | Connective tissue between two cords |
| 3 | Beneke..... | .. | .. | ..... | 0 | 0 | 0 | |
| 4 | Bernstein, J. M.: Tr. Path. Soc. London **57**: 318, 1906 | 16 yr. | M | 1st-3d lumbar | 0 | 0 | 0 | |
| 5 | von Bonome..... | Newborn | .. | Lower lumbar | + | 0 | 0 | Connective tissue and cartilage between two cords |
| 6 | Bruce, A.; McDonald, S., and Pirie, J. H. H.: Rev. Neurol. & Psychiat. **3**: 709, 1905 | 31 yr. | F | Lumbar and sacral | 0 | 0 | 0 | Sheath of dura between two cords |
| 7 | Chiari..... | 17 yr. | .. | Lumbar | + | + | 0 | |
| 8 | Cruveilhier..... | .. | .. | 12th dorsal, 1st-2d lumbar | 0 | 0 | + | |
| 9 | Fischer..... | Newborn | .. | Upper cervical | + | + | 0 | Kyphoscoliosis on basis of deformity of vertebral bodies; clubfoot |
| 10 | Fischer..... | Newborn | .. | 9th dorsal | 0 | 0 | + | Fusion of medially directed arches with bony process |
| 11 | Fox..... | 76 yr. | F | Lumbar | 0 | 0 | 0 | Lumbar kyphoscoliosis; clubfoot on right |
| 12 | Gross, S. W., and Sachs, E.: Arch. Surg. **28**: 874, 1934 | .. | .. | ..... | + | 0 | 0 | |
| 13 | Hamby [4]..... | 20 yr. | F | 3d-4th lumbar to end | + | 0 | + | Diagnosed during life |
| 14 | Henneburg and Westenhöfer: Berl. klin. Wchnschr. **50**: 2379, 1912 | 17 yr. | F | Lumbar | + | 0 | 0 | Clubfoot on left; weakness and bilateral paresthesia of left leg |
| 15 | Herren and Edwards (current case) | 23 yr. | F | Lumbar and sacral | + | 0 | + | |
| 16 | Humphry: J. Anat. & Physiol. **20**: 585, 1886 | Newborn | .. | Lumbar | 0 | 0 | + | Two bony processes in midline of cord not described |
| 17 | Humphry: Ibid.. | .. | .. | Lumbar | 0 | 0 | + | |
| 18 | Humphry: Ibid.. | Fetus | .. | Lumbar | + | 0 | + | Cord not described |
| 19 | Humphry: Ibid.. | .. | .. | ..... | + | .. | + | |
| 20 | Humphry: Ibid.. | .. | .. | Dorsal 5th-9th | + | 0 | + | |
| 21 | Humphry: Ibid.. | 16 days | M | Lumbar and sacral | 0 | 0 | + | |
| 22 | von Lenhossek... | 6 mo. fetus | .. | Lumbar | 0 | 0 | 0 | |
| 23 | Lipshutz, B.: Arch Neurol. & Psychiat. **4**: 16, 1920 | 35 yr. | M | Upper lumbar | 0 | 0 | 0 | |
| 24 | von Monakow, C.: Neurol. Centralbl. **15**: 995, 1896 | Fetus | .. | Most of cord | 0 | 0 | 0 | Cyclops |

* Cases 1, 5, 9, 10, 11, 25, 26, 27, 28, 31, 33, 34, 39, 40 and 41 were taken from the review by Zalewska-Ploska [2]; cases 2, 3, 7, 8, 22, 29, 35 and 36, from Bruce, McDonald and Pirie [1] and case 30 from Weil and Matthews.[3]

*Data on Forty-Three Cases of Diplomyelia Reported in the Literature—Continued*

| Case | Author | Age | Sex | Level of Doubling | Spina Bifida | Meningocele or Meningomyelocele | Osseous or Osseochondromatous Process | Comment |
|---|---|---|---|---|---|---|---|---|
| 25 | Naegeli..... | Newborn | .. | Lower part of cord | + | + | 0 | Cyclops |
| 26 | von Recklinghausen | 31 yr. | F | Lumbar | 0 | 0 | 0 | Sheath of dura between the two cords |
| 27 | von Recklinghausen | .. | .. | Sacral | + | 0 | + | Acrania and anencephalus |
| 28 | von Recklinghausen | .. | .. | Sacral | + | 0 | + | |
| 29 | Rosenberg..... | 3 yr. | .. | Middorsal | + | 0 | 0 | |
| 30 | Schenk..... | 5 mo. fetus | .. | ..... | + | 0 | 0 | Acrania |
| 31 | Seelert..... | .. | .. | Lower part of cord | 0 | 0 | 0 | No clinical symptoms referable to the spinal cord |
| 32 | Smith, E.: J. M. Research **38**: 479, 1918 | 5 days | M | Upper dorsal | + | 0 | + | |
| 33 | Steiner..... | 3½ mo. | .. | Sacral | + | 0 | 0 | |
| 34 | Sulzer..... | .. | .. | Lumbar | 0 | 0 | 0 | Intervening cartilaginous mass |
| 35 | Taruffi..... | Newborn | .. | Lumbar | + | 0 | 0 | First lumbar spinal arches directed medially to join in midline and separate canal into halves |
| 36 | Theodor..... | 2 days | .. | Lumbar | + | + | 0 | |
| 37 | Weber, F. P.: Brit. M. J. **1**: 1106, 1928 | 51 yr. | .. | Lumbar and sacral | 0 | 0 | 0 | |
| 38 | Weil and Matthews [2] | 5 mo. | .. | Lower dorsal | + | + | 0 | |
| 39 | Wietung..... | 5 days | .. | Lumbar | + | + | 0 | |
| 40 | Wietung..... | 3 days | .. | Lower dorsal | + | + | + | Lower vertebral bodies defective and separated as much as 4 cm. from each other |
| 41 | Wietung..... | 10 days | .. | Lower dorsal | + | + | 0 | Connective tissue septum between cords; vertebral bodies defective or lacking |
| 42 | Zalewska-Ploska [2] | 50 yr. | F | Midlumbar | + | 0 | 0 | |
| 43 | Zalewska-Ploska [2] | 8 mo. | F | Lumbar and sacral | + | + | + | Diagnosed during life |

The spinal column frequently, though by no means always, presents an anomalous appearance. In more than half of the cases reviewed the condition was associated with spina bifida; the majority of these were of the occult variety. It is interesting to note that in practically all of the cases in which there was an associated meningocele or meningomyelocele, death occurred at any early age. This suggests the possibility that a complication, such as an infection of the sac, may have been responsible for the early death. The spinal canal may show an abnormal appearance, varying from a moderate degree of dilatation at the level of the duplication of the cord to partial doubling. The latter was seen in about a quarter of the cases reviewed and was accomplished by a midline cone-shaped

osseous or osseochondromatous process with its base attached to or continuous with the dorsal aspect of one or of several vertebral bodies and with the apex directed dorsally into the lumen of the spinal canal. In the majority of cases there was a single process, but occasionally there were two or more, one lying above the other. In several of the cases in which this osseous or osseochondromatous process was not seen there was a band of connective tissue lying in the midline between the two spinal cords. This connective tissue occasionally contained some cartilage. In about 10 per cent of the cases of diplomyelia reviewed there were defects in the vertebral bodies. These consisted either of underdevelopment or complete absence of several bony segments.

The meninges are commonly duplicated at the level of the diplomyelia, so that each cord possesses its own covering coat. This appears to be universally true of the pia but not of the arachnoid, while the dura showed doubling in somewhat less than half of the cases.

The extent of duplication of the spinal cord is usually limited to about ten spinal segments, and the level of the doubling usually lies below the middorsal region. In only 2 cases was the lesion above this point. In all the cases reviewed the two cords lay lateral to each other, and we were unable to find any case in which one cord lay ventral to the other and in which an artefact could be absolutely ruled out. Each cord appeared to have been rotated through an angle approaching 90 degrees, so that the ventral gray columns of the two cords faced each other and the ventral fissures lay more or less in the same frontal plane. In several cases each cord was associated with four primary nerve roots, a pair of ventral and dorsal roots lying laterally and a pair situated medially. In most of these cases, however, the lateral roots were well formed, while the medial, when present, were rudimentary and, as we shall indicate later, were associated with underdeveloped gray columns. The structure of each of the two cords is fundamentally similar to the definitive spinal cord. Each shows a central canal surrounded by gray substance arranged in an H shape. There are four gray columns, two ventral and two dorsal, one pair lying laterally and the other medially. The lateral columns are well developed and presumably functioning, while the medial set is small, with poorly formed ganglion cells scattered haphazardly. Usually each cord has a well developed ventral fissure. In cords that show doubling the lesion usually continues to include the sacral segments, but in a few cases there was fusion of the halves in the lower levels, with reestablishment of a single, well formed cord.

Usually, above the level of the diplomyelia the cord shows no apparent abnormality, but in a few cases it exhibited hydromyelia of a mild degree, and in 1 instance this abnormality was well established.[3] In an occasional case there was an abnormal condition of the brain, such as anencephalus,

hydrocephalus or cyclops, but these conditions are the exception rather than the rule. Anomalies involving organs other than the spine and central nervous system are sometimes observed, the most common of which is clubfoot. In 1 case double kidneys and ureters were found.

There appear to be no specific clinical features referable to diplomyelia, and in most cases the associated lesions, such as clubfoot, spina bifida and meningocele, receive most of the attention. Weakness of a leg, anesthesia or paresthesia was noted in a few cases, but it is difficult to prove that the diplomyelia per se was responsible for these clinical abnormalities. It has been demonstrated that diplomyelia may exist without any evidence of malfunction of the central nervous system and may appear as an accidental finding at autopsy. In only 2 of the 42 cases studied was the diagnosis of diplomyelia made during the life of the patient.[6] One of these was Hamby's case, that of a 20 year old woman who showed exaggerated knee jerks and saddle anesthesia. At operation the cord was found to be bifid and separated by a bony process with a dermoid cyst attached at its apex.

In the case reported here diplomyelia was suspected during the life of the patient on the basis of operative findings, as will be indicated in the report which follows.

## REPORT OF A CASE

*Clinical History.*—An unmarried white woman, aged 23 years, was first admitted to the Boston City Hospital in 1934 for treatment of intermittent ulcers on the dorsum of the left foot. At this time examination revealed a left-sided clubfoot, which was cold and cyanotic, and a small ulcer at the base of the fourth toe. The muscles of the left leg were atrophied. The left ankle and knee jerks were absent. The spinous processes were described as "split" from the level of the eleventh thoracic vertebra to that of the third lumbar vertebra. Roentgen examination of the spine showed apparent fusion of the eighth, ninth, tenth and eleventh thoracic vertebral bodies and spina bifida of the lumbar portion of the spine.

The patient was subjected to an exploratory operation on the spinal canal at the lower thoracic and lumbar levels. Although complete visualization of structures was not accomplished, because of hemorrhage and shock, the latter requiring rather prompt termination of the operation, certain observations were made. Spina bifida was present. The laminas and the spine of the eleventh thoracic vertebra seemed to be inverted, being directed ventrally and bisecting the spinal cord. The ventral extremities of the inverted laminas were attached to the dorsal aspect of the vertebral body. These were removed, and it was observed that the distal half of the spinal cord, which previously had not pulsated, began to pulsate freely. After an uneventful course the patient was discharged from the hospital.

Fourteen weeks prior to her final admission, April 5, 1938, she began to suffer from headaches and vomited on two occasions. Loss of memory and subsequently lethargy developed.

The patient exhibited apathy, somnolence and poor memory. The right pupil was larger than the left. The right lower extremity showed paresis, no reflexes

6. Hamby.[4] Zalewska-Ploska.[2]

were present in the left leg, and the right triceps and radial reflexes were absent. There was questionable choking of the left optic disk. A harsh systolic pulmonic murmur, nontransmitted, was heard.

The total red blood cell count varied from 4,700,000 to 6,300,000 per cubic millimeter. The total white blood cell count was 12,000 per cubic millimeter, of which 50 per cent were polymorphonuclear leukocytes. The Hinton test of the blood was negative. An electrocardiogram was interpreted as showing myocardial disease. Several lumbar punctures revealed the initial pressure varying from 190 to 250 mm. of water, with normal dynamics. The total protein varied from 47 to 82 mg. per hundred cubic centimeters. The Kahn test of the spinal fluid was negative. The colloidal gold reduction on one occasion was 0122221000.

Throughout her stay in the hospital the patient showed intermittent fever, the temperature rising as high as 104 F. Blood cultures were negative. Stiffness of the neck developed with marked choreoathetotic movements and cogwheel rigidity of the four extremities.

Five weeks after her admission, her temperature rose to a peak of 104.4 F.; she became stuporous, the spinal fluid pressure rose to 330 mm. of water, and decerebrate rigidity developed. She died on May 12, 1938, the day following the development of this episode.

The final clinical diagnoses were: (?) subacute bacterial endocarditis with cerebral emboli; (?) encephalitis lethargica; (?) tumor of the third ventricle.

*Postmortem Examination.*—The gross anatomic diagnoses were as follows: local reduplication of the spinal cord; glioma of each thalamus, of questionable type; internal hydrocephalus involving lateral ventricles; congestion of the lower lobe of the left lung.

On external examination the body was that of a fairly well developed and nourished young white woman. The left foot lay in a flexed position and was distinctly shorter than the right. It was covered by scaly, grayish brown skin of tough texture. The second toe was absent, and over the head of the first metatarsal was an ulcer, measuring 2 cm. in diameter and covered by a grayish brown crust. In the midline of the back, corresponding with the lower thoracic region, was a vertical scar, measuring 8.5 cm. in length. The spine revealed deformities of the ninth, tenth and eleventh thoracic vertebral bodies (fig. 1*A*). The tenth body appeared underdeveloped and almost completely invested by intervertebral cartilage inferiorly, superiorly and dorsally. It lay in the ventral portion of the spinal column and did not reach the wall of the spinal canal. Instead, it was separated from the canal by an isthmus of spongy bone which blended with the ninth thoracic vertebra superiorly and the eleventh inferiorly. At the junction of this bony isthmus with the body of the ninth thoracic vertebra there projected a conical process of bone into the lumen of the vertebral canal (fig. 2*A*). The process lay in the midline and measured about 1.2 cm. in height and 2 cm. in diameter at its base. Its histologic appearance was identical with that of a normal vertebral body. The spinal canal showed moderate lateral widening at the level of the bony process.

The cervical and upper thoracic segments of the spinal cord were not remarkable.

Beginning at the level of the seventh thoracic segment and continuing into the sacral region, the cord was present in the form of two components, the diameter of each being about half that of a normal cord. At the uppermost level of the separation the two halves were connected by loose pial tissue. The cords gradually moved apart so that at the level of the ninth thoracic body the two halves were

separated by the bony process already described (fig. 2 *B*). At this level each cord was enclosed in a separate sheath of dura. Below the level of the bony process the two cords were contained in one sheath of dura. They came into

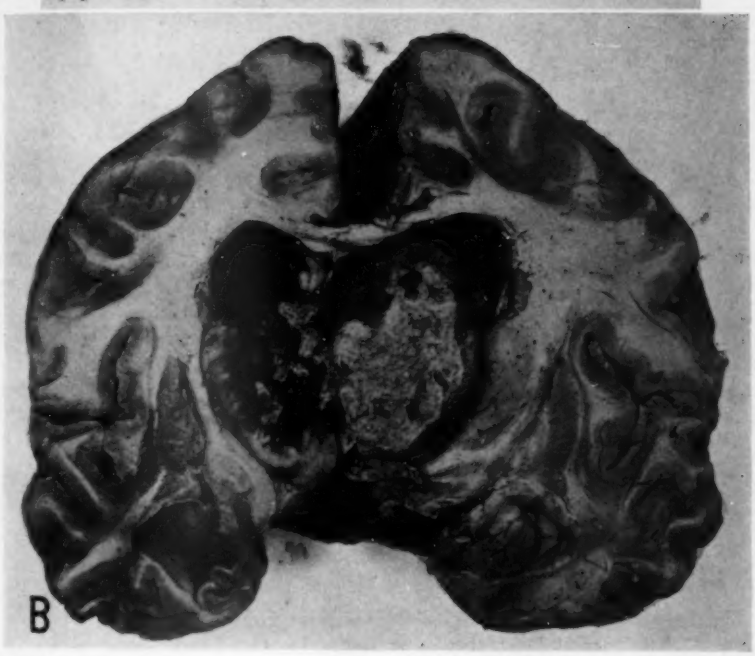


Fig. 1.—*A*, gross photograph of the bisected spinal column. The tenth thoracic vertebral body is small and does not reach the spinal canal. A bony conical process (pictured also in figure 2) is shown arising from an isthmus of bone between the ninth and eleventh vertebral bodies. *B*, coronal section of the cerebral hemispheres through the basal ganglions. The thalamus of each side is distinctly enlarged by the presence of neoplastic tissue bulging into the cavities of the lateral ventricles.

closer apposition and were again held together by only a small amount of pial tissue and an occasional band of intercommunicating white matter. Each cord appeared to have been rotated through an angle of about 90 degrees, so that the anterior columns of each cord faced each other. In one segment, at the level of the bony process, where two sheaths of dura were present, a dentate ligament

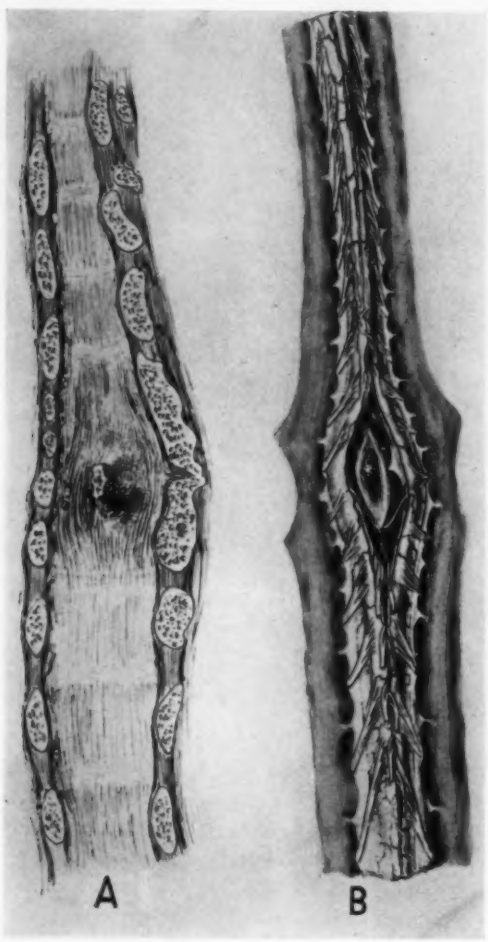


Fig. 2.—*A*, drawing of the spinal canal. The specimen is viewed from behind forward. The conical bony process arising from the anterior wall of the canal is shown. Here there is moderate widening of the canal. *B*, drawing of the spinal cord. The cord is double in its lower half. At the upper levels of the separation the two cords are separated by the bony process seen in *A*. At this level each cord possesses a separate sheath of dura.

arose from the medial aspect of each cord. The spinal cord was cut at several levels, and sections were stained for myelin and for Nissl's substance, as well as with hematoxylin and eosin.

Microscopically, the cervical portion of the cord was normal in all respects (fig. 3*A*). A section from the seventh thoracic segment showed a fairly large central canal which distorted the central gray substance (fig. 3*B*). At the tenth thoracic segment the cord was present in two parts, each containing a central canal. The central gray substance was elongated laterally, and a thin strip of white substance covered the dorsal gray bridge. In the lateral aspect of each cord the dorsal and ventral gray columns were well developed. In addition, the right cord showed a rudimentary medial dorsal column with entering fibers. At the level of the twelfth thoracic segment there was complete reduplication of the cord (fig. 3*C*). Each half was enclosed in a separate sheath of pia-arachnoid and showed a central canal. There were two ventral and two dorsal gray columns in each cord, and a well defined ventral fissure. The cords appeared to lie almost at right angles to the normal position, so that the ventral fissures faced

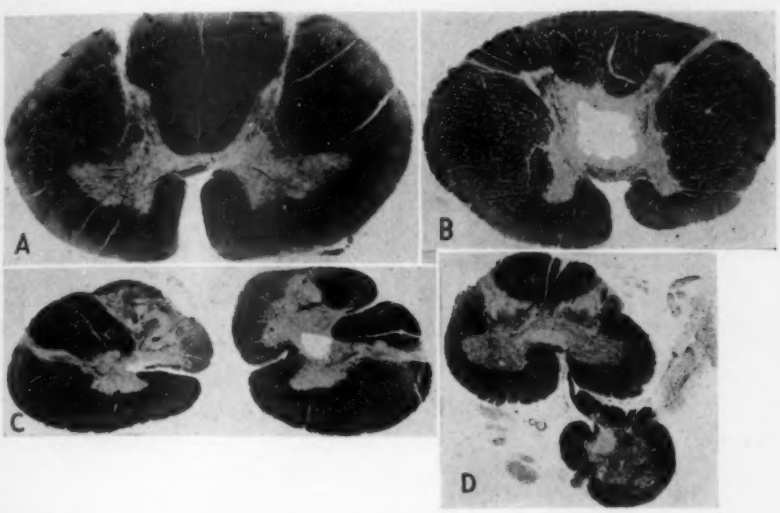


Fig. 3.—Cross sections of spinal cord stained for myelin by the Weigert-Pal method: *A*, cervical cord. The cord is essentially normal in appearance. *B*, thoracic cord above the level of doubling. There is moderate hydromyelia. *C*, lower part of thoracic cord. The cord is double. Each cord has a central canal, four gray columns and an anterior fissure. The cords are rotated so that the anterior fissures lie facing each other. In each cord the lateral set of gray columns is well developed, while the medial set is rudimentary. *D*, sacral cord. The right cord appears complete. The left contains a central canal. The gray substance is eccentric, and the ganglion cells are arranged haphazardly.

each other in a frontal position. In the sacral region there were present two cords of unequal size (fig. 3*D*). The right cord, which was the larger, showed ganglion cells in its four well developed columns. In the left cord there were no well defined gray columns, the ganglion cells lying in an ill defined mass of gray substance eccentric to the central canal.

The brain weighed 1,350 Gm. and showed evidence of increased intracranial pressure in the form of flattening and widening of the cerebral convolutions and moderate coning of the cerebellum. Each thalamus was enlarged and diffusely

infiltrated by soft tumor tissue, which varied from yellow to pale pearly gray (fig. 1 *B*). The right thalamus was larger than the left, measuring 5 cm. from above downward and 3 cm. from side to side. The lateral ventricles were moderately increased in width.

Microscopic sections of the tumor revealed that it was a well differentiated glioma with numerous intercellular neuroglial fibrils. The nuclei varied in shape from round to fusiform. Mitotic figures were present in small numbers. In a few fields there were occasional giant cells. The major part of the tumor tissue was typical of astrocytoma.

The lungs showed evidence of mild congestion in the left lower lobe. The remaining organs were entirely negative grossly and histologically.

## COMMENT

The symptoms and signs which arose shortly before the patient's death, namely, somnolence, apathy, loss of memory, choking of the disks, cogwheel rigidity, athetosis and fever, were undoubtedly related to the tumor involving each thalamus and had no apparent relation to the diplomyelia. On the other hand, as early as four years before the patient's death there were observed absence of ankle and knee jerks in the left leg and cyanosis and coldness of the left foot, together with transitory ulcers. It seems reasonable to associate this group of symptoms and abnormal physical signs with the diplomyelia. However, it is difficult to prove that the diplomyelia per se was responsible for these signs and symptoms because others have observed this anomaly without any demonstrable functional abnormality. Therefore, one may justifiably suppose that the concomitant deformities of the spine might have been the underlying cause of these clinical manifestations, although it is impossible for us to state exactly which one of the spinal deformities was responsible for the mechanism operating. Pressure from either the bony process or the pair of inverted spinal arches invites speculation. However, there was no appreciable alteration in the appearance of the left leg after surgical removal of the inverted arches, nor did we observe at autopsy any evidence of atrophy of the spinal cords due to pressure.

The development of diplomyelia cannot be explained on the basis of arrested development of the spinal cord, for there is no normal embryonic stage in which the cord is double. Consequently, it appears that diplomyelia develops as the result of an abnormal step in the process of differentiation of the central nervous system.

Does diplomyelia represent a primary alteration of the spinal cord, or does it develop secondary to an abnormality of the spine? The latter suggestion would not appear tenable for the following reasons: Diplomyelia, although commonly, is nevertheless not always, associated with an abnormal spinal column, and during embryonic life the cord develops long before the spinal column. It seems logical, therefore, to consider diplomyelia as a primary malformation and the associated abnormalities of the spinal column as secondary to the anomlies of the central nervous system.

In chick embryos one sometimes observes a change in the neural plate which may have some bearing on the problem of diplomyelia. As the lateral extremities of the plate approach the midline dorsally, preliminary to fusing, they may be directed ventrally for a moderate distance. Usually however, they apparently retreat dorsally, fuse and complete the formation of the tube. However, if the lateral extremities of the neural plate should continue ventrally, they might ultimately fuse with the ventral portion of the plate on either side of the midline and so yield two medullary tubes. Two tubes formed in this way might develop into two definitive spinal cords. The two cords could continue to lie closely opposed, or each might migrate laterally for varying distances, the space between them becoming filled in with as yet undifferentiated mesenchyma. If the distance between the two cords should be small, the intervening mesenchyma might merely develop into pial tissue, but if more space should exist, more mesenchyma might appear and additional elements, such as arachnoid, dura or even bone, might develop.

If this explanation is accepted, a basis for the presence of a complete sheath of meninges for each cord, as well as for the presence of the intervening bony process described in our case, may be seen. The presence of the pair of inverted spinal arches fusing in the midline may be considered as a reaction on the part of the mesenchyma, producing a bony canal for each cord. At the level of this deformity the vertebral body was single but the spinal canal may be considered double. In this respect the midline bony process would represent fusion of right and left medial spinal arches, and the lateral peduncles of the secondary arches would be those of the primary arch, spread further apart.

The atrophic medial, ventral and dorsal columns of the double cords deserve some mention. While the doubled cord in our case may be considered an incipient form of twinning, the rest of the body did not show any duplication. Since the peripheral nerves develop independently of the spinal cord, there were in all probability no nerves formed to connect with the medial sets of gray columns with the exception of the segment at the level of the bony process. These columns in turn, having no apparent function, probably never developed fully.

## SUMMARY

The case of a 23 year old woman with diplomyelia involving the lower part of the spinal cord is reported. There was associated spina bifida. A bony process in the midline extending to the arches of the eleventh thoracic vertebra divided the vertebral canal in two. There were clubfoot on the left, absence of knee and ankle jerks, and coldness and cyanosis of the left foot with intermittent trophic ulcers. Death was due to a neoplasm involving each thalamus, diagnosed as glioma.

Diplomyelia, variously termed double, duplicated or reduplicated spinal cord, or diastometamyelia, is characterized by the presence of two more or less perfectly formed spinal cords at varying levels. The lesion is discovered at ages varying from fetal to adult life and is distributed equally between the sexes.

The spinal column may be normal, but spina bifida occurred in about two thirds of the cases reviewed. In a quarter of the cases there was an osseous or osseochondromatous process in the midline separating the two cords.

Each cord shows a central canal and two ventral and two dorsal gray columns, but the lateral columns are usually the only ones associated with primary nerve roots.

There may be no symptoms directly referable to the lesion.

Diplomyelia probably represents a slight degree of twinning, the primary changes occurring in the medullary tube. The abnormalities of the spinal column, when present, suggest a mesenchymal reaction to the presence of two spinal cords.

# TRIPLICATION OF THE LARGE INTESTINE

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Some authors have mentioned the vague possibility of a triple colon, chiefly in reference to birds, rather than to human beings, but until now no case seems to have been reported in the medical literature. The gastrointestinal tract is a fertile field for various and curious congenital malformations, which are a fascinating study to both the surgeon and the pathologist. The hindgut, however, is not a common site of errors in development. It is true that one may find all types of abnormality described, from congenital absence of the colon to congenital atresias, diverticula, reduplications and Hirschsprung's disease, but triplication of the large intestine has apparently not been reported heretofore. This extremely rare congenital anomaly was encountered in the postmortem examination of a baby girl who died at the age of 11 months.

## REPORT OF A CASE

*Clinical History.*—This infant was admitted to the Montreal Children's Hospital, July 27, 1939, at the age of 1 week. She was born at full term and weighed 7 pounds, 16 ounces (3,629 gm.) at birth. It was then noted that she had absence of the vagina and external genitalia, exstrophy of the bladder and questionable imperforate anus. Since birth the baby had lost weight, and for two days prior to admission she had vomited continually. The family history was unimportant.

On admission to the hospital the liver and spleen were palpable. There were no external genitals and no vagina. The posterior aspect of the bladder was seen on the anterior abdominal wall, representing complete exstrophy. The ureters were patent and opened onto this surface. Superiorly and laterally above the bladder were symmetric ventral hernias. The anus appeared to be slightly more anterior than usual and the orifice somewhat lax; through it fecal material passed intermittently.

Roentgen examination of the abdomen and of the rectum with a catheter inserted failed to disclose any abnormalities other than gas shadows.

While in the hospital the baby gained weight. The vomiting ceased, and further feedings were well taken. Bowel movements were frequent and loose and averaged four to six daily. The child was discharged October 2. On readmission, fifteen days later, she had a septic fever, ranging between 97 and 100 F. (axillary). The urine was now turbid, containing traces of albumin, 50 to 60 white blood cells per high power field and bacteria. The child had lost weight, weighing 6 pounds, 10 ounces (3,005 Gm.).

Succeeding months saw a continuance of the septic temperature but a gradual gain in weight and at all times normal bowel movements. Pyelitis had now arisen,

From the Department of Pathology, McGill University.

which was persistent and did not respond to any therapy, including the administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine).

Early in March 1940, increasing distention of the abdomen became obvious, and there was obstinate constipation, which could be relieved only by enemas. The temperature ranged between 97 and 105 F., at times remaining elevated for days.

Late in April the respiration increased, cyanosis became marked, and the child died, April 23, with bronchopneumonia.

*Postmortem Examination.*—The body was 58 cm. long and weighed 4,610 Gm. There was ectopia of the bladder with complete absence of the anterior wall; the posterior wall was represented by a thickened, reddish, granular area, 6 by 8 cm. The ureters opened onto the posterior wall superiorly, running downward in an inferior and medial direction. Below the ureters the primitive trigon could be seen as a slight triangular thickening of the mucous membrane. The posterior wall of the urethra extended inferiorly below the trigon for a distance of 5 mm., the anterior wall being absent. Laterally and somewhat inferiorly, the nonfused segments of the clitoris were encircled by thickenings of the dermis, these being the rudimentary labia. Posteriorly there was a single anal orifice, around which the skin was roughened, reddened and excoriated.

The right lung was light reddish pink, subcrepitant throughout and rather firm and nodular in the right upper and lower lobes. The heart was normal.

The recti muscles had not fused along the medial borders, the intervening defect being covered by fibrous tissue. The rami of the pubic bones had not fused in the midline to form a symphysis pubis but remained widely separated.

The abdominal organs were in normal position and presented no abnormalities except those to be described.

The small intestine showed no lesion, and the single ileocecal valve opened into a large, somewhat conical cecum. Posteriorly there was a single appendix. Exploration of the colon revealed that it was located in the usual site but was markedly dilated, the enlargement beginning in the ascending portion and increasing gradually in the transverse and descending portions. At the rectosigmoid junction this dilated bowel ended in a cul-de-sac, measuring 6 cm. in diameter, its position being in the midline of the body. On section the lumen was filled with soft fecal material, and the wall was hypertrophied in the descending portion, measuring 4 mm. in thickness at the blind end.

Posterior and just superior to the ileocecal valve were two small apertures, which opened freely into two completely distinct undilated lumens which lay in the posterior and medial wall of the dilated blind channel just described. The latter was paralleled throughout its entire course by these two supernumerary colons, which at all times remained on the antimesenteric border. At the rectosigmoid junction, instead of ending in a blind pouch, these two additional channels passed medial to the cul-de-sac and entered into the single rectum through two patent orifices, 5 mm. apart. Free communication existed between the rectum and the anus.

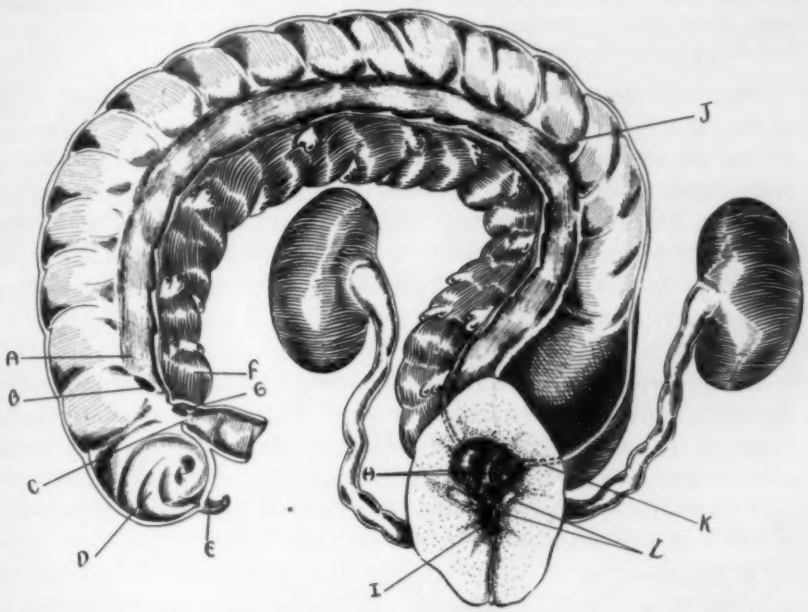
On section both patent colons were of about the normal size for a year old child, and their walls were of average thickness. Both contained fecal material. Each measured approximately 1.5 cm. in diameter. The lumens of all three colons were lined by mucous membrane. Nowhere was there any defect in the septums between the colons, and they ran as separate tubes from the cecum to the rectum.

A single layer of peritoneum encased the three intestines. There were no taeniae or haustra on the external surface, but abundant appendices epiploicae. Blood ves-

sels ran through the leaves of the mesentery, supplying first the blind colon, while additional branches arose from these and coursed over the first and second patent colons.

Displaced laterally by the distended blind colon were the rudimentary internal genital organs. On the left, the tube and ovary were compressed against the pelvic wall and were connected with a narrowing fibrous cord, which represented the müllerian duct. On the right, the same condition existed except that the ovary and most of the tube had herniated into the canal of Nuck. There was no fusion between the müllerian ducts to form a uterus.

Dilated ureters ascended from the bladder, pursuing a tortuous course into the pelves of the kidneys. Urine was readily expressed through the ureteral orifices.




Drawing of the gross specimen of triple colon, kidneys, ureters, ectopic bladder and external genitalia: *A*, first patent colon; *B*, aperture of first patent colon; *C*, ileocecal valve; *D*, cecum; *E*, appendix; *F*, second patent colon; *G*, aperture of second patent colon; *H*, ureteral orifices; *I*, anus; *J*, blind colon laid open; *K*, termination of blind colon; *L*, rudimentary labia.

The kidneys were similar, each weighing 35 Gm. The capsules stripped readily, exposing a smooth, dark red cortex. On the cut surfaces the cortex averaged 3 mm. in thickness, and the normal markings of the cortex and medulla were conspicuous. There was slight bilateral hydronephrosis.

*Microscopic Examination.*—The heart, spleen, liver, adrenals, pancreas, marrow, thymus, aorta, stomach and pituitary showed no lesion.

In the section of the lungs there were extensive hyperemia, edema, purulent bronchitis and in the upper and lower lobes of the right lung early bronchopneumonia.

The kidneys showed passive congestion, areas of pyelonephritic scarring around the glomeruli with lymphocytic infiltrations, slight compression of the medulla, and foci of round cells beneath intact pelvic epithelium.

Sections of the colons taken at various levels showed the same histologic picture at each site. The mucosa was smooth throughout; the glands of Lieberkühn were abundant and lined by many goblet cells. The lamina propria was well developed, containing scattered lymphoid follicles. The muscularis mucosae consisted of circular and longitudinal coats, both of which were hypertrophied in the distal segment of the blind colon. Each of the three colons was surrounded separately by circular muscle. The longitudinal muscle, however, formed a single layer enclosing all three colons, and in none of the sections examined did it aid in forming the septal walls between the lumens, which were composed only of mucosa and circular muscle. No taeniae could be found microscopically. Along the serosa were innumerable appendices epiploicae. Blood vessels, lymphatics and nerves followed a normal course and distribution.

*Anatomic Diagnosis.*—The conditions were triple colon; nonfusion of the pubic bones; nonfusion of the müllerian ducts; congenital absence of the uterus and vagina; nonfusion of the segments of the clitoris; rudimentary vulvar labia; diastasis recti abdominis; ectopia of the bladder; bilateral hydroureters and hydronephrosis; bilateral chronic pyelonephritis; acute purulent bronchitis; pulmonary edema, and acute bronchopneumonia of the upper and lower lobes of the right lung.

## COMMENT

In surveying the literature one finds little to aid one in an attempt to explain triplication of the large intestine. The nearest approach to the condition is duplication. These two congenital anomalies seem to be closely allied, having certain similarities and differences. Perhaps, then, by a discussion of duplication and the outstanding embryologic explanations for it, some conclusions may be formulated.

Many examples of double intestine have been reported, not only in man but in the bird, cow and ox. In the human being duplication is usually coexistent with extensive skeletal and visceral abnormalities. In the case just described a skeletal abnormality existed in the form of nonfusion of the pubic bones, and visceral malformations were present in the genitourinary tract. This is the first point of similarity.

One of the earliest reports of double hindgut is that of a double cecum referred to by Gould and Pyle,[1] which appeared in the early eighteenth century "Ephemerides" of the Leopoldine Academy (published in Frankfurt, Germany, 1712-1717). Calder,[2] in 1733, was the

1. Gould, G. M., and Pyle, W. L.: Anomalies and Curiosities of Medicine, Philadelphia, W. B. Saunders Company, 1897, p. 287.

2. Calder, J., in Medical Essays and Observations, Revised and Published by a Society in Edinburgh, Edinburgh, Ruddimans, 1733, vol. 1, p. 203.

first to describe duplication of the small intestine. Later Meckel [3] referred to a fetus with two ceca described by Boerhaave.

Duplication of the distal portion of the hindgut alone may exist. Lockwood,[4] in 1822, reported a case of double descending colon: "The two tubes were upon the same plane, the smaller one nearer the vertebral column. Each possessed appendices epiploicae." He referred to the smaller one as a diverticulum. Möller [5] described reduplication of the colon from the rectosigmoid junction to the anus, combined with other anomalies. Roux de Brignolles [6] discovered a double pelvic colon while operating on a patient for appendicitis. In a case of Wright's [7] there was developmental duplication of the sigmoid colon.

An example in which the first portion of the hindgut was affected was seen by Läwen [8]; the ileum divided into two ceca, one ending in a blind pouch and the other continuing into the ascending colon. Ballance [9] operated on a child for imperforate anus. "To obtain a clear field for the perineal operation, a temporary colostomy in the transverse colon was performed. Four months later the colostomy was closed, and at this operation it was found that doubling of the colon extended nearly, or quite as far as the caecum." This was confirmed by roentgenograms and microscopic sections from the surgical specimen.

Complete doubling of the hindgut, however, is quite rare. Ombrédanne [10] examined a patient who had duplication of the vulva, clitoris, anus, rectum, colon and cecum and nonfusion of the pubic bones. These observations were confirmed by careful clinical and roentgen examination. Bar [11] reported another such patient brought to him with an imperforate anus, in whom there was a single cecum but a double colon from it to the rectosigmoid junction. There was no anus, but instead two ectodermal dimplings, the one on the right being the larger. Autopsy supported the clinical findings. One colon terminated in a cul-de-sac at the rectosigmoid junction, while the other narrowed distally into a stringlike process which spread in a fan-shaped manner over the superior surface of the bladder. Section showed that each colon had its own mucosa, lamina propria and circular layer of muscularis mucosae. The longitudinal layer of muscle encased the two and ran into the intervening

3. Meckel, J. F.: Tabulae anatomico-pathologicae, Leipzig, J. F. Gleditsch, 1822, pt. 3, p. 13.
4. Lockwood, C. B.: Brit. M. J. **2**:574, 1882.
5. Möller, H.: Frankfurt. Ztschr. f. Path. **8**:151, 1911.
6. Roux de Brignolles: Ann. internat. de chir. gastro-intest. **8**:19, 1914.
7. Wright, G.: Proc. Roy. Soc. Med. (Sect. Surg.) **13**:119, 1920.
8. Läwen, A.: Beitr. z. path. Anat. u. z. allg. Path. **55**:575, 1913.
9. Ballance, H.: Proc. Roy. Soc. Med. **23**:1570, 1930.
10. Ombrédanne, L.: Mém. Acad. de chir. **62**:747, 1936.
11. Bar, P., and de Hervilly, M.: Obstétrique **14**:81, 1909.

septum, mingling with the circular fibers which formed the septal wall. Other congenital anomalies were spina bifida, two bladders, each with one ureter opening into it, two urethras, nonfusion of the scrotum and a rudimentary penis.

Proof that there may be combined duplication of the large and small intestine is furnished by a case described by Aitkin.[12]

> Towards its termination the ileum bifurcated, forming two complete separate tubes of equal calibre and length (17 cm. long), ending on opposite sides of a somewhat conical caecum. Below these two ileocaecal junctions the wall of the caecum showed a deep sulcus running in a longitudinal direction and subdivided this portion of the gut into two parts, with a small vermiform appendix about 2 cm. in length at the extremity of each. From the caecum there issued an apparently single great intestine, somewhat contracted, but otherwise normal in external appearance, as far as the middle of the descending colon. At this point a deep furrow appeared in the situation of one of the longitudinal muscular bands and persisted down to the termination of this gut. Upon section of the colon it was found that the lumen of this part of the intestine was divided by a septum into two completely separate channels which opened externally, one at the normal anal aperture, the other within the vulvar cleft just in front of the posterior commissure. The intestine was double from the lower part of the ileum onwards.

Microscopically, the septum was lined by mucosa and submucosa of the two colons proximally, while distally there was doubling of all coats in the septum except for the longitudinal muscle, and traces of it could be seen between the circular layers of muscle in the septum.

These cases proved conclusively that duplication of the large intestine may occur in any portion or in entirety, and in conjunction with a similar malformation in the small intestine. The fact that doubling may occur throughout offers a second similarity to the triple colon in the present case.

A third point of similarity is seen in the histologic picture. Those examples of double colon which were described microscopically showed, like the triple colon in the present case, a mucosa, a lamina propria and a layer of circular muscle surrounding each. Those of Aitkin and Bar had longitudinal muscular coats which surrounded the two colons, running into the septum somewhat, but not actually forming a part of the wall. This picture is not unlike that of the longitudinal muscle surrounding the triple colon. Further analogous conditions were noted in regard to the peritoneum, mesentery and blood vessels.

Hudson [13] offered six theories to explain the embryologic conditions of reduplication of the intestine:

> (1) Atavism. Reversion to an earlier phylogenetic form based on the occurrence of bifid ceca in certain fowl and multiple diverticula in fish.

12. Aitkin, A. B.: Glasgow M. J. **78**:431, 1912.
13. Hudson, H. W.: New England J. Med. **213**:1123, 1935.

(2) Twinning, in which case "the stimulation to reduplication, although acting at an early stage of cell division, has affected a certain section only of the embryo" (Edwards).

(3) Through the development of a median septum. . . .

(4) Sequestration of a segment of the intestinal tube . . . (Evans).

(5) Persistence and alterations of the vitelline duct or Meckel's diverticula in their several forms.

(6) The nodules of Lewis and Thyng. These investigators found very regularly in pig, rabbit, and human embryos, nodules of epithelial cells occurring along the course of the esophagus, stomach, and intestine which become vacuolated and may be separated from or be in continuity with the lumen of the intestinal tract. Normally, these disappear or coalesce to form a part of the lumen of the digestive tube but they may persist.

Hudson found 18 cases of reduplication described in the literature, to which he added 3.

The first of these theories, that of atavism, offers a solution on the basis of comparative anatomy. It is unlikely, however, that this conception explains "tripling" any more than it explains "doubling," and, furthermore, the former has been spoken of as being only a possibility.

The second theory, that of twinning, offers a possible clue to the explanation of this case. Perhaps tripling in the early stages of development of the ovum and cell division could confine itself to the gut alone instead of producing three complete embryos.

Evans [14] stated that "many cases reported as duplications of the intestinal tract were either developmental diverticula or enterogenous cysts." A triple colon would not fall into either of these categories. Segmental sequestration of the intestine might apply in some instances, but not when three colons have been formed, extending from the cecum to the rectum.

Fitz [15] regarded duplication of the gut as an elongated diverticulum, resulting from growth of the remains of the vitelline duct, and, indeed, remnants of the vitelline duct have been found with great variance of position along the intestinal tract. Meckel's diverticulum, however, is found usually in the last 6 feet (183 cm.) of the small intestine and rarely elsewhere. It is most difficult to see how a portion of the vitelline duct or Meckel's diverticulum could ever produce duplication, much less triplication, of the large intestine.

This leaves only the theory of Lewis and Thyng.[16] In their paper it was emphasized that nodular clumps of epithelial cells were observed only along the course of the small intestine and that along the large intestine none could be found. In accepting this idea, therefore, to

14. Evans, A.: Brit. J. Surg. **17**:34, 1929.

15. Fitz, R. H.: Am. J. M. Sc. **88**:30, 1884.

16. Lewis, F. T., and Thyng, F. W.: Am. J. Anat. **7**:505, 1907-1908.

explain duplication of the small intestine, it must be admitted that it is an even more remote possibility as regards the large bowel.

Dr. A. J. Dalton, of the department of anatomy of McGill University, prepared the following opinion of the case reported here.

From the point of view of the embryologist, this case presents several features of interest:

1. The exstrophy of the bladder. This indicates that some interference with the normal development of the urogenital sinus occurred shortly after the 10 mm. stage.

2. The presence of short, blindly ending oviducts, together with the complete absence of the uterus and vagina. This clearly indicates that a gross disturbance in the development of the genital system has occurred. The müllerian ducts, which begin to form at the 10 mm. stage, normally make connection with the urogenital sinus through the genital cord at about 38 mm. Thus the factors involved in the maldevelopment of the urinary system may well have been responsible for the anomalous condition of the genital system.

3. The malformation of the colon. This is difficult to explain on embryologic grounds.

Each of the three duplications of the colon is surrounded by a separate, distinct layer of circular muscle, while the longitudinal muscle, devoid of taeniae, forms a single tunic common to all three. According to Lineback,[17] the circular muscle of the colon appears first near the developing anal canal, at the 30 mm. stage, and becomes complete throughout the colon at the 35 mm. stage. The longitudinal layer does not begin to form until about the 46 mm. stage and does not reach its definitive condition until the 105 mm. stage is attained. This considerable difference in the time of the appearance of the two layers of the tunica muscularis accounts for their peculiar arrangement. The longitudinal subdivision of the colon must have occurred at a relatively early stage, when the precursors of the circular muscle were appearing but before the development of the longitudinal layer. One possible explanation for this reduplication of the colon may be found in the results frequently obtained when portions of young chick embryos are transplanted to the chorioallantoic membrane of older hosts. Under these relatively abnormal conditions grafts of gut tissue frequently develop branching tubules and reduplications (Dalton[18]). It is suggested that the unfavorable conditions thought to be responsible for the maldevelopment of the urinary and genital system may also have induced the formation of the triple colon.

## SUMMARY

A case of triplication of the large intestine is reported. Eleven examples of duplication of the hindgut have been collected from the literature and certain similarities to the present anomaly noted, but no previous report of triple colon has been encountered.

17. Lineback, P. E.: Contrib. Embryol. **11**:33, 1920.
18. Dalton, A. J.: J. Exper. Zool. **71**:17, 1935.

# Case Reports

## SPINAL EPIDURAL ABSCESS ASSOCIATED WITH ACTINOMYCOSIS

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Spinal epidural abscesses are most frequently associated with Staphylococcus. Streptococcus is the next most frequent cause. Pneumococcus,[1] the typhoid bacillus,[2] Bacillus pyocyaneus [3] and Oidium coccidioides [4] have been reported as causative agents in isolated cases. Wilson and Kammer [5] reported a spinal epidural abscess in a Negro 22 years old who had actinomycosis. No reference is made to bacteriologic or mycologic studies of this spinal abscess.

The following report of a case is made because of the rarity of spinal epidural abscess associated with actinomycosis.

### REPORT OF A CASE

A man 54 years old had a dull pain in the region of the right scapula and night sweats for six weeks. He had a hard, dry paroxysmal cough, productive of slight amounts of sputum, for four weeks. Ten years previously, at the Memorial Hospital for the Treatment of Cancer and Allied Diseases, he had had a tumor mass, 10 cm. across, removed from the right cervical region. This was diagnosed histologically as Hodgkin's disease, and 500 roentgens of roentgen radiation was directed to the right cervical region. He had had no recurrences.

The significant findings on his admission to the New York Hospital on Nov. 2, 1939, were: temperature, 38.6 C. (101.5 F.); pulse rate, 104; respirations, 20; blood pressure, 116 systolic and 62 diastolic. The patient was a well developed, chronically ill white man of 54 years. The superficial lymph nodes were not palpable. There was a well healed scar over the right side of the neck. The tissue beneath this was dense and nodular. The chest was symmetric. In the right interscapular region posteriorly there were dulness, diminished tactile fremitus, tubular breath sounds and fine rales, with increased voice sounds. The remainder of the lung fields showed no changes. The heart and abdomen were normal. There was no evidence of any gross anatomic lesion of the central nervous system.

The white blood cell count was 12,000, with moderate polymorphonuclear leukocytosis. The blood platelets were normal. Serologic tests for syphilis were negative. The urine showed no significant change.

From the Department of Pathology of the Cornell University Medical School and the New York Hospital.

1. Browder, J., and Meyers, R.: Am. J. Surg. **37**:4, 1937. Schick, B.: Wien. klin. Wchnschr. **22**:1185, 1909. Peters: Deutsche med. Wchnschr. **32**:1151, 1906.

2. Raymond and Sicard: Bull. et mém. Soc. méd. d. hôp. de Paris **22**:860, 1905.

3. Schmidt: Deutsche Ztschr. f. Chir. **58**:566, 1901.

4. Dickson, E. C.: Arch. Int. Med. **16**:1028, 1915. Rand, C. W.: Arch. Neurol. & Psychiat. **23**:502, 1930.

5. Wilson, G., and Kammer, A. G.: M. Clin. North America **18**:287, 1934.

The clinical impression was that the patient had Hodgkin's disease either of the upper lobe of the right lung or of the mediastinal lymph nodes, causing compression of the bronchus to the right upper lobe and atelectasis. Bronchoscopic examination on the eighth hospital day showed no intrabronchial neoplasm. The bronchus to the right upper lobe was retracted upward. The patient was given 1,025 roentgens to the mediastinum as a therapeutic test, without change in the symptoms or in the lesion itself as evidenced by physical signs or by roentgen examination.

Nine weeks after admission the patient suddenly became unable to pass urine. Progressive weakness of both lower extremities and of the trunk rapidly developed, with loss of sphincter control and sensory defects below the dermatome supplied by nerves from thoracic segment 6 on each side. A diagnosis of a lesion involving the spinal cord at the level of thoracic segment 6 was made. The patient became worse and died on the seventy-ninth hospital day. He had had an irregular fever, cough and sputum throughout the course of his illness. A complete postmortem examination was done three hours after death.

*Autopsy.*—The body was that of a well developed but poorly nourished white man. There was a well healed surgical scar, 4 cm. long, in the right supraclavicular region. The tissue beneath this was fibrotic. The superficial lymph nodes were not palpable.

Pleural Cavity: In the right pleural cavity was 1,150 cc. of cloudy fluid. There was a pocket of empyema in the upper posteromedial part of the right pleural space, with osteomyelitis of the first and second ribs on the right side and of the fourth, fifth and sixth thoracic vertebrae. The left pleural cavity was partly obliterated by dense fibrous adhesions.

Lungs: These together weighed 1,440 Gm.; the upper and middle lobes of the right lung were dense, and the normal architecture of the cut surface was replaced by dense gray-white translucent fibrillar tissue mottled with yellow. In the upper lobe was a moderate number of abscesses, measuring up to 1 cm. across. Some of these could be traced to bronchi. Several of the most peripheral abscesses communicated with the empyematous cavity posteriorly. The lower lobe of the right lung was atelectatic. There was no significant change in other parts of the lungs.

Liver: This weighed 2,120 Gm. In the dome of the right lobe was a multiloculated abscess, 50 mm. across. This was filled with thick yellow-green pus and communicated with the subdiaphragmatic space to form a localized abscess. There were several similar abscesses in other parts of the right lobe.

Vertebral Column: There was osteomyelitis of the fourth, fifth and sixth thoracic vertebrae with erosion into the spinal canal. Acute purulent inflammation in the epidural space in the region of the fourth and fifth dorsal vertebrae communicated through a tract between the fourth and fifth dorsal vertebrae with the empyematous cavity on the right.

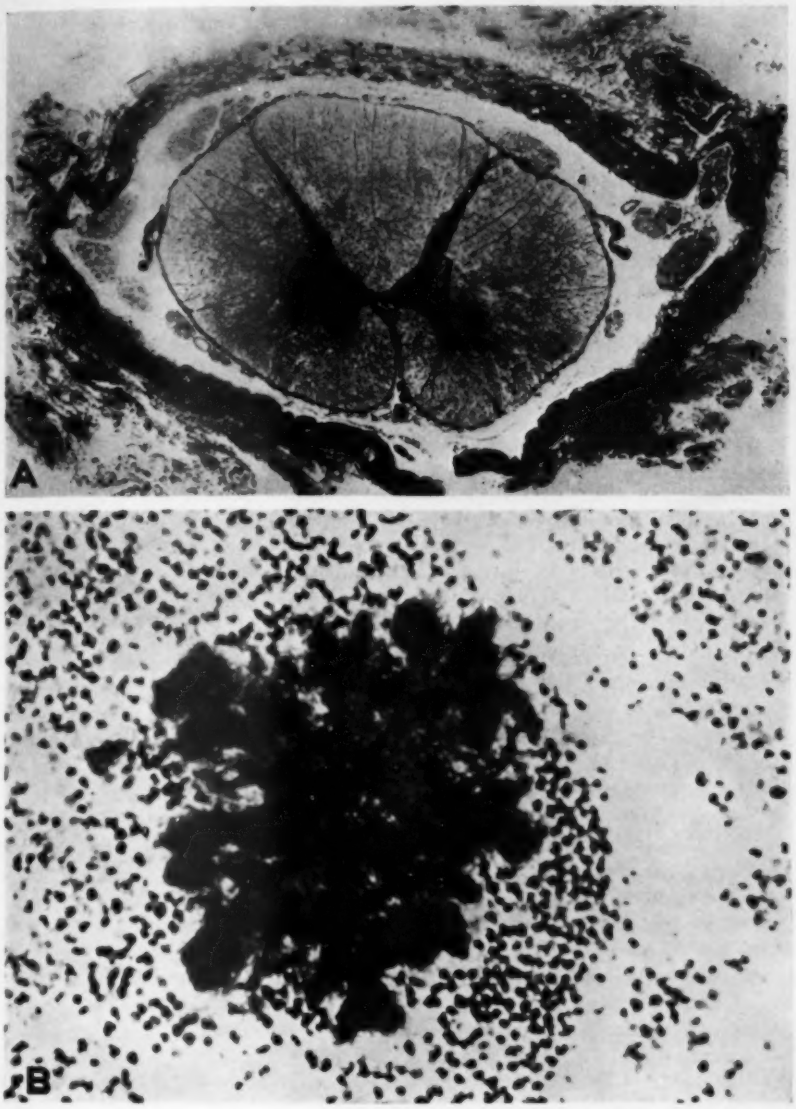
Brain: The circle of Willis was slightly sclerotic. There was slight cortical atrophy of both frontal lobes and of the upper parietal lobules. The cerebral veins of both hemispheres were engorged with blood. Slight internal hydrocephalus was present.

Spinal Cord: No nodules were visible under the dura. In the upper thoracic region was an area of softening in the spinal cord, and the dura was thickened in this region by a friable mass attached to its outer surface.

No significant changes were found in other viscera.

*Microscopic Examination.*—Lung: In the upper lobe of the right lung the normal architecture was replaced by a loose cellular vascular connective tissue, in which were numerous small irregular glandlike spaces lined by cuboidal epithelium. Numerous abscesses were filled with polymorphonuclear leukocytes, and in them

were numerous colonies of Actinomyces. The walls of the bronchi were infiltrated heavily with lymphocytes and a few plasma cells. No evidence of Hodgkin's disease was found.




*A*, section through the epidural abscess in the thoracic region of the spinal cord containing colonies of Actinomyces; degeneration of the white matter of the spinal cord; × 10. *B*, a high power photomicrograph of one of the colonies of Actinomyces in the exudate; × 250. The sections are stained by Masson's trichrome method.

Liver: The liver cords were separated by sinusoids distended with blood. Numerous confluent abscesses contained colonies of Actinomyces.

Spleen and Lymph Nodes: These showed no evidence of Hodgkin's disease.

Marrow: There was slight hyperplasia of the myeloid and moderate hyperplasia of the erythroid elements. No Hodgkin's disease was recognizable.

Spinal Cord: Sections through the extradural mass and spinal cord in the thoracic region showed an abscess lying on and invading the dura (figure, *B*). The abscess contained many colonies of Actinomyces. On the under surface of the dura were a few colonies of the same organism with a slight exudate of cells containing many mononuclear cells as well as some polymorphonuclears. In the exudate below the dura there were a number of phagocytes containing blood pigment and cells. A number of lymphocytes were in the meshes of the pia-arachnoid and around the nerve roots attached to the spinal cord. Colonies of Actinomyces could be seen in the subarachnoid space in places. The cord itself showed early degenerative changes, the white matter having a spongy character in a few places. Few cells remained in the anterior horns; they showed degenerative changes, having a few palely staining Nissl granules and indistinct nuclei. Glia nuclei seemed to be increased throughout the gray matter.

No other significant changes were found.

*Anatomic Diagnosis.*—Actinomycosis with fibroid pneumonia of the upper and middle lobes of the right lung; multiple abscesses in the upper lobe of the right lung, in part communicating with the pleural cavity; localized empyema over the posterior part of the right upper lobe; fibrinopurulent pleurisy on the right (1,150 cc.); atelectasis of the lower lobe of the right lung; osteomyelitis of the first and second ribs on the right and of the fourth, fifth and sixth thoracic vertebrae, with erosion into the spinal canal and formation of an epidural abscess; abscesses in the liver; erosion of the hepatic abscess into the subdiaphragmatic space.

# PYELONEPHRITIS WITH BILATERAL STRICTURES OF RENAL CALICES AND ASSOCIATED HYPERTENSION

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Strictures of the renal calices in the absence of tuberculous pyelonephritis or renal calculi is an uncommon condition. A case of chronic pyelonephritis with bilateral strictures of the renal calices was discovered at autopsy.

## REPORT OF A CASE

A 48 year old white man, unmarried, was admitted, July 24, 1939, with complaints of blurring of vision of six months' duration and shortness of breath of two months' duration. He had had frequency of urination and nocturia since early in 1934. In 1935 a cystoscopic examination revealed mild chronic cystitis, and retrograde pyelograms (fig. 1) showed bilateral bifid pelves. In October 1936, following a chest cold of two weeks' duration, acute urinary retention developed, with chills, fever and vomiting. He catheterized himself several times during five days of self treatment, after which he came to this hospital.

The blood pressure was slightly elevated. There was tenderness in the left costovertebral angle; the prostate was enlarged and indurated on the right side; the bladder contained 1½ ounces (45 cc.) of residual urine, in which there were numerous pus cells and red blood cells. A diagnosis of pyelitis was made. After three days in the hospital his fever and symptoms subsided, and on the seventh day he was discharged. Since 1936 the urinary frequency and nocturia had increased in severity, and there was diminution in the size and force of the stream, with occasional tenesmus and burning on urination. In May 1939 he spent twelve days in another hospital, where a cystoscopic examination and retrograde pyelograms showed grade 2 enlargement of the median lobe of the prostate, which projected into the bladder. Eight ounces (240 cc.) of residual urine was found at the time of the cystoscopic examination, although the patient had voided thirty minutes previously. Ureteral catheters were passed on each side for a distance of 30 cm. There was no flow from the right side. The flow from the left side was free, and a phenolsulfonphthalein test gave 115 cc. of urine with 7 per cent of the dye after twenty minutes. The pyelogram was considered "unsatisfactory." A urea clearance test May 15, 1939 showed 15 per cent of normal clearance. The patient stated that he knew that he had had high blood pressure for the preceding four years. Since July 1934 he had been seen in the outpatient department of the hospital on several occasions because of epigastric distress and pain, which radiated to both shoulders and to the back, but roentgenograms of the gastrointestinal tract and gallbladder did not show evidence of disease. He had had diphtheria and scarlet fever in childhood and gonorrhea in 1907. The positive findings July 24, 1939 were as follows: The patient was well developed, well nourished, of short stature and sthenic build, and he appeared acutely ill. The skin was warm and moist. The retinas were edematous, and the disks were blurred and hazy. The retinal arteries showed marked narrowing at the arteriovenous

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crossings, and there were numerous flame-shaped fresh hemorrhages and cotton wool exudates along the arteries. The mouth was edentulous, and dental plates were worn. There was a uriniferous odor to the breath. Coarse rales were heard at the base of each lung posteriorly. The heart was enlarged to the left and downward; the blood pressure was 212 systolic and 130 diastolic. The liver was enlarged 2 fingerbreadths below the costal margin and was slightly tender. Rectal examination showed grade 2 enlargement of the prostate with slight induration of the lateral margins. The reflexes were hyperactive. There was slight

Fig. 1.—Retrograde pyelogram taken Feb. 7, 1935.

pitting edema of the ankles. The patient was given rest in bed, a salt-free diet, digitalis and theophylline with ethylene diamine U. S. P. (aminophylline) but showed no improvement. On August 1 he was drowsy and disoriented. On August 3 he was comatose, his reflexes were diminished on the right side, and his eyes were deviated to the left. The temperature, which had been normal, now rose to 102 F. On August 5 he died.

The laboratory findings obtained on previous admissions to this hospital and to other hospitals are shown in the table. The Kline exclusion test of the blood was negative.

The clinical diagnoses were essential vascular hypertension, malignant type; hypertensive retinopathy; hypertensive renal disease with uremia; median bar prostatic enlargement with obstruction.

*Autopsy* (eight hours after death).—The body was that of a well developed, fairly well nourished white man, apparently of the stated age of 48. The skin was pale lemon yellow. The right border of the heart was 5 cm. to the right of the midsternal line; the left border was 10 cm. to the left of the midsternal line. The lower border of the liver was 4 cm. below the costal margin in the midclavicular line and 6 cm. below the xiphoid process. The urinary bladder was distended, its upper border reaching midway from the pubis to the umbilicus. The heart weighed 800 Gm. The left ventricle measured 30 mm. in thickness; the right ventricle, 8 mm. The right lung weighed 700 Gm.; the left lung, 500 Gm. There was a calcified subpleural nodule, 7 mm. in diameter, in the upper portion

*Blood Pressure Readings, Blood Nonprotein Nitrogen Values, Blood Counts and Urinalyses Obtained from Records of Various Hospitals Attended by Patient from 1930 to 1939*

| Date | Blood Pressure | Blood Nonprotein Nitrogen, Mg. per 100 Cc. | Blood Counts: Hemoglobin, Gm. per 100 Cc. | Blood Counts: Erythrocytes | Blood Counts: Leukocytes | Urinalyses: Specific Gravity | Urinalyses: Albumin | Microscopic Observations |
|---|---|---|---|---|---|---|---|---|
| 1930 | 120/ 80 | .. | .... | ..... | ..... | ..... | .. | ..... |
| Jan. 1934 | ..... | .. | 10.0 | 4,400,000 | 6,500 | ..... | .. | ..... |
| Jan. 1935 | 136/ 90 | 29 | 16.0 | 4,490,000 | 10,800 | 1.011 | 0 | Two leukocytes |
| Oct. 1936 | 152/ 92 | 39 | 11.0 | 3,460,000 | 20,200 | 1.015 | +++ | Numerous erythrocytes and leukocytes |
| Nov. 1937 | 174/110 | .. | .... | ..... | ..... | 1.014 | + | Occasional erythrocyte and leukocyte; occasional granular and hyaline casts |
| May 1939 | 230/114 | 58.5<br>64.4 | 12.5 | 4,500,000 | 5,300 | 1.006<br>1.012 | Trace<br>++ | Occasional erythrocyte and leukocyte; many granular casts in one specimen |
| July and Aug. 1939 | 220/144 to 165/130 | 115 to 200 | 8.3 | 2,780,000 | 8,250 | 1.008 to 1.014 | ++ to +++ | From 0 to 8 leukocytes |

of the lower lobe of the right lung. The lower lobes of both lungs were congested. The liver was enlarged and weighed 1,675 Gm. It cut with slightly increased resistance; the cut surface was light brown, and the architecture was easily made out. The gallbladder was attached to the liver and omentum by firm fibrous adhesions, and its wall and mucosa were slightly thickened. The spleen weighed 150 Gm. The pancreas weighed 100 Gm. The adrenals were of average size and of usual shape and consistency.

The right kidney was of the usual size and shape but was soft and fluctuant. On section (fig. 2) the parenchyma was replaced by dilated cystlike calices filled with clear light yellow fluid. The parenchyma of the kidney was compressed beneath the capsule and between the cystlike spaces and measured from 2 to 4 mm. in thickness. The lining of the dilated calices was whitish and smooth. At the points of origin of the calices from the pelvis there was fibrous scarring with complete obliteration of the urinary passage. The renal capsule stripped with some increase in resistance, revealing a pale, smooth but lobulated surface. The kidney

weighed 75 Gm. after the fluid had been drained. The ureter was of average caliber and patent throughout, but its walls were thickened. The left kidney was of average size and externally showed a constriction in its midportion, which incompletely divided the organ into an upper half measuring 5 by 5 by 3 cm. and a lower half measuring 5 by 4.5 by 3.2 cm. The upper half was soft and fluctuant, and on section it resembled the right kidney and revealed dilated cystlike calices filled with clear yellowish fluid, between which the compressed parenchyma measured 2 to 5 mm. in thickness. The main calix of this half of the kidney, at the point of its origin from the pelvis, was the seat of a fibrous scar which

Fig. 2.—Bilateral hydronephrosis, hydroureter on the left, dilatation of the bladder and enlarged median prostatic lobe.

resulted in complete obliteration of the lumen. The lower half of the kidney was made up of firm, light brown parenchyma, the markings of which were indistinct. The main calix was slightly dilated, and at its points of origin from the pelvis it showed a constriction of its lumen, which measured about 2 mm. in diameter or about one third of the normal diameter. The caliber of the left ureter was uniformly dilated to about twice normal. The mucosa was smooth and glistening. The capsule of the left kidney stripped with increased resistance. The capsular surface of the lower half was finely granular. The left kidney weighed 100 Gm. after the fluid had been drained.

The urinary bladder (fig. 2) was distended and contained approximately 700 cc. of clear amber-colored urine. The wall of the bladder was thickened, and there were trabeculations, which were raised and prominent. The mucosa was gray and opaque. The prostate was slightly enlarged, firm and nodular, and the median lobe projected into the bladder for a distance of 1 cm. above the internal urethral orifice. The seminal vesicles were indurated and contained brown mucoid material. The vasa efferentia were thickened and indurated. The testes and epididymides were of normal appearance. The gastrointestinal tract showed moderate hyperemia.

The brain weighed 1,350 Gm. and appeared swollen and pale. On section of the cerebrum, there were seen throughout the cortex, especially in the left postcentral region and in the left occipital lobe, multiple areas of punctate softening with surrounding discoloration.

*Microscopic Examination.*—Section through the compressed parenchyma of the right kidney showed much young and old fibrous tissue and diffuse infiltration by lymphocytes and plasma cells. Practically all of the glomeruli were hyalinized, but an occasional glomerulus contained blood and had a thickened capsular wall. The lumens of the tubules were compressed or completely obliterated. Section through the pelvis and calices showed scar tissue infiltrated with lymphocytes and some plasma cells.

Section through the upper and lower halves of the left kidney showed slight compression atrophy, which was more marked in the upper half. Variously altered glomeruli were seen, including hypertrophic, inflammatory, contracted and hyalinized glomeruli. Areas of dilated, sometimes hypertrophic tubules alternated with areas of compressed atrophic tubules, and in both areas regenerated tubular epithelium was seen. In the lumens of all varieties of the tubules erythrocytes and hyaline debris were seen. The collecting tubules contained hyaline casts, and in the terminal ducts of Bellini large, finely granular casts were seen. There was a focal distribution of lymphocytes and plasma cells, particularly in the atrophic areas. Sections through the strictures showed scar tissue with scattered infiltration by lymphocytes and some plasma cells. In all of the sections of the kidneys the smaller arteries and the arterioles showed greatly thickened walls with reduplication of the internal elastic membranes and subendothelial proliferation of fibrous tissue or hyalinization. A number of arterioles showed obliterating endarteritis. In the walls of many arterioles there were necrotizing lesions and edema.

Sections of the prostate, urinary bladder and gallbladder showed microscopic evidence of chronic inflammation.

The muscle fibers of the heart were hypertrophic.

The lungs showed bronchopneumonia.

Sections from other organs showed arterial and arteriolar sclerosis and hyperemia, and, in addition, the brain showed numerous small extravasations of blood and softening of brain tissue around the smaller arteries of the cortex, and localized edema. Necrotizing and hyalinizing changes were seen in the walls of the arterioles of the spleen, pancreas and adrenals.

The final anatomic diagnosis was chronic pyelonephritis with bilateral strictures of the renal calices, internal hydronephrosis and compression atrophy of the right kidney and of the upper half of the left kidney; chronic prostatitis with hypertrophy of the median lobe of the prostate; chronic cystitis with hypertrophy and dilatation of the bladder; slight hydroureter on the left; bronchopneumonia; hypertrophy and dilatation of the heart; generalized arteriolar sclerosis with necrotizing changes; miliary cortical encephalomalacia; edema of the brain; chronic cholecystitis; obsolete primary tubercle of the lower lobe of the right lung.

COMMENT

Clinically this case was diagnosed as one of chronic glomerular nephritis at another hospital in May 1939 and as one of malignant hypertension with arteriolar nephrosclerosis at the William J. Seymour Hospital in July 1939. Retrograde pyelograms taken in 1935 showed bilateral bifid pelves with some narrowing of the infundibular portion of the upper calices of both kidneys. Retrograde pyelograms taken in May 1939 were considered unsatisfactory since they showed no filling of the calices on the right side and partial filling of only the lower calix on the left side. The observations at autopsy show that the second pyelogram was an accurate representation of the state of the kidneys at that time. At autopsy scar tissue had completely shut off the calices from the pelvis on the right side, and on the left side the only calix which drained into the pelvis was dilated, owing to a cicatricial stenosis of its infundibular portion.

Cicatricial narrowing of the infundibula leading to the calices and resulting in caliectasis is a relatively common finding in chronic pyelonephritis according to Braasch [1] and Engel.[2] Braasch stated that temporary obstruction in one or two of the infundibula, due to scarring, is probably the cause of the recurring attacks of acute pyelonephritis which are frequently observed in patients with chronic pyelonephritis. However, no reference to atresia of the infundibula, such as was present in this case, was found in the recent literature.

Another interesting feature of this case is that progressive severe hypertension began to develop approximately one year after the onset of urinary symptoms. Several articles have been published during the past few years regarding the association of hypertension with chronic pyelonephritis. In 1932 a case of malignant hypertension and chronic pyelonephritis was reported.[3] Weiss, Parker and Robb [4] observed that patients with malignant hypertension frequently gave a history of chronic pyelonephritis, pyelitis or perinephritic abscess. Butler [5] stated that hypertension is not infrequently associated with pyelonephritis before there is any appreciable diminution in renal function. Longcope [6] found hypertension in a high percentage of clinical cases of advanced pyelonephritis but failed to find a generalized arteriolar sclerosis in the cases in which autopsies were performed. Commenting on these articles, Goldblatt [7] stated that it is probable that the hypertension associated with chronic pyelonephritis occurs only when there is associated vascular sclerosis or when the inflammatory disease produces the same effects on renal circulation as does the vascular disease. Kimmelstiel and Wilson [8]

1. Braasch, W. F.: J. Urol. **39**:1, 1938.

2. Engel, W.: Cleveland Clin. Quart. **6**:217, 1939.

3. Vascular Nephritis, Malignant; Pyelonephritis, Cabot Case 18032, New England J. Med. **206**:129, 1932.

4. Weiss, S.; Parker, F., and Robb, G. P.: Ann. Int. Med. **6**:1599, 1933.

5. Butler, A. M.: J. Clin. Investigation **16**:889, 1937.

6. Longcope, W. T.: Ann. Int. Med. **11**:149, 1937.

7. Goldblatt, H.: Surgery **4**:483, 1938.

8. Kimmelstiel, P., and Wilson, C.: Am. J. Path. **12**:99, 1936.

demonstrated two types of inflammatory lesions of focal distribution occurring in the glomeruli in pyelonephritis. One of these is due to an extension of the inflammatory condition, while the other lesion is independent of the inflammatory condition and is indistinguishable from the focal glomerulitis which is found in malignant hypertension. Goldblatt and Butler, as well as Barker and Walters,[9] referred to cases of unilateral pyelonephritis with hypertension in which there was a prompt return of blood pressure to normal after the diseased kidney had been removed.

Goldblatt and his co-workers[10] produced chronic hypertension in dogs and monkeys by constricting the renal arteries. This work has been confirmed by a number of investigators, among whom may be mentioned Page,[11] Wood and Cash,[12] Wilson and Pickering,[13] who worked with rabbits, and Wilson and Byron,[14] who worked with rats. Moritz and Oldt,[15] in studying arteriolar changes at autopsy in various organs of the body in 100 hypertensive and 100 nonhypertensive persons, found a remarkable correlation between chronic hypertension and arteriolar sclerosis in the kidneys.

In the light of these observations it may be of interest to attempt to correlate the observations at autopsy with the clinical history in this case. Symptoms of disease of the urinary tract were present in 1934. The pyelograms taken in February 1935 show narrowing of the infundibular portion of the upper calices in both kidneys. Since the narrowing was present in both kidneys it is not likely to have been due to spasm. In October 1936 there was an acute episode of pyelonephritis, and numerous pus cells and red blood cells were found in the urine. Blood pressure readings were normal in 1930 and in January 1935 but showed beginning elevation in October 1936 and a progressive rise after this date.

At autopsy the lower pole of the left kidney, which showed only slight hydronephrosis, had the characteristic finely granular surface of primary contracted kidneys. Microscopic sections of this portion of the kidney showed severe arteriolar sclerosis, a variety of degenerative changes in the glomeruli and a reduction in the number of intact glomeruli. Some glomeruli were apparently normal but hypertrophied. some were of the "hypertensive" type described by McGregor,[16] and others showed focal or general inflammatory changes. Tubular changes also were identical with those described by Loomis[17] as occurring in

9. Barker, N. W., and Walters, W.: Proc. Staff Meet., Mayo Clin. **13**:118, 1938.

10. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: J. Exper. Med. **59**:347, 1934. Goldblatt, H.: ibid. **65**:671, 1937.

11. Page, I. H.: Am. J. Physiol. **112**:166, 1935.

12. Wood, J. E., Jr., and Cash, J. R.: J. Clin. Investigation **15**:543, 1936.

13. Wilson, C., and Pickering, G. W.: Clin. Sc. **3**:343, 1938.

14. Wilson, C., and Byron, F. B.: Lancet **1**:136, 1939.

15. Moritz, A. R., and Oldt, M. R.: Am. J. Path. **13**:679, 1937.

16. McGregor, L.: Am. J. Path. **6**:347, 1930.

17. Loomis, D.: Arch. Path. **22**:435, 1936.

hypertension. In addition, there were areas of dense lymphocytic infiltration of greater extent than is commonly seen in arteriolar nephrosclerosis.

While it is possible that the vascular disease was independent of the pyelonephritis in this case, it is my opinion that the pyelonephritis was the primary cause of the vascular disease. The sequence of events is believed to have been as follows: bilateral pyelonephritis, renal arteriolar sclerosis producing renal ischemia, hypertension, generalized arteriolar sclerosis, scarring and stricture formation of the calices of both kidneys, internal hydronephrosis, compression atrophy of the right kidney and of the upper half of the left kidney, uremia, localized necrotizing arteriolitis.

## SUMMARY

A case is presented of chronic pyelonephritis with bilateral stricture of the calices which produced internal hydronephrosis and was accompanied by progressive severe hypertension, which terminated in death from uremia. No report of a case of atresia of the infundibula due to nontuberculous pyelonephritis was found in the literature.

# GLOMERULUS-LIKE NEOPLASTIC STRUCTURES IN A CARCINOMA OF THE KIDNEY

MILTON D. BOSSE, M.D., PITTSBURGH

In a recent article Owen [1] proposed the term "glomeruloma" for a tumor of the kidney which he had observed, and collected from the literature 8 other renal tumors, which he placed in the same category. The purpose of this paper is to report a renal carcinoma with microscopic features similar or identical to those of the tumor reported by Owen and to discuss the desirability of placing this tumor in a category separate from renal carcinoma.

## REPORT OF A CASE

A white woman 39 years of age, with a diagnosis of miliary tuberculosis, came to autopsy two and one half hours after death.

The right kidney presented a white nodular firm mass of tissue, 5 cm. in diameter, projecting 1.5 cm. above the surface and occupying the middle third of the kidney. On section the mass was more extensive than appeared externally. It infiltrated the surrounding parenchyma, without encapsulation. It was located mostly in the cortical zone, where there was an irregular area of reddish brown necrosis, 1 cm. in diameter, but it also extended through the pelvic mucous membrane. In addition, both kidneys contained a number of nodules, 3 to 6 mm. in diameter, of similar tissue. Very numerous miliary metastases were present throughout both lungs, and the tumor also involved the pleural surfaces, tracheobronchial lymph nodes, liver, adrenals and a number of abdominal lymph nodes.

Microscopic examination of the growth frequently showed rounded or oval masses of cells in a glomerulus-like arrangement amidst either abundant dense or loosely arranged fibrillar stroma. Some masses were larger and some were smaller than normal glomeruli, and some were about the same size as glomeruli. They had a lining of cells which was sometimes single layered and sometimes piled up irregularly. The lining and the central masses of cells were similar and usually connected in one or more areas. Most of these structures were avascular, but some had poorly defined capillaries containing a few leukocytes or red blood cells. Many of the tumor cells were fairly large, polygonal and moderately dark, but as a whole they varied considerably in size, shape and staining and often had poorly defined cell boundaries. The nuclei varied also in size and shape and many were hyperchromatic. Mitotic figures were rare. Other than the glomerulus-like structures, the tumor had no particularly unusual features, although seeming transitional stages from normal tubules to tumor tubules were seen, and, in addition, one glomerulus was seen the tuft of which apparently contained tumor cells. The resemblance of certain of the tumor structures to glomeruli is shown in the photomicrographs (*A*, *B* and *C* in the figure).

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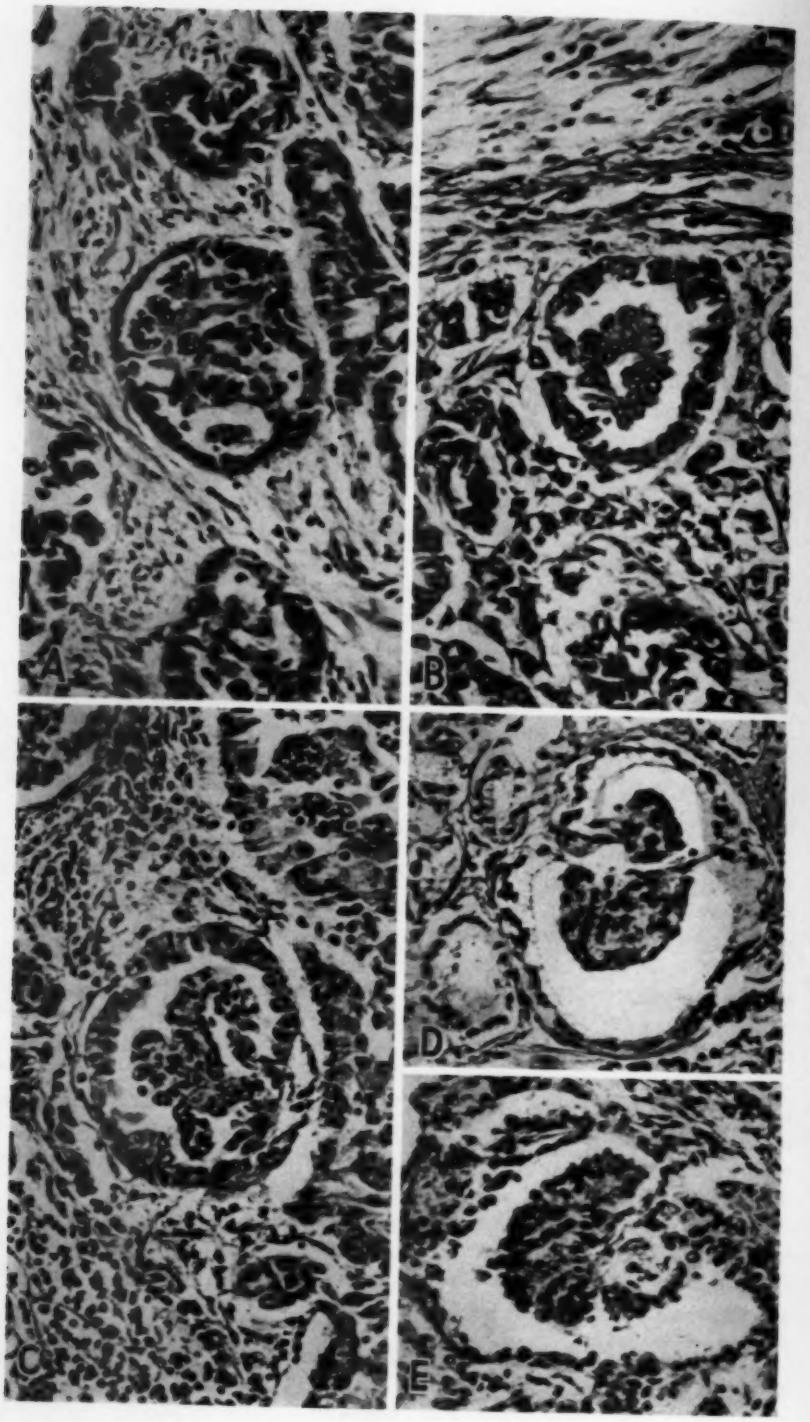
From the Western Pennsylvania Hospital Institute of Pathology; Dr. Ralph R. Mellon, director.

1. Owen, C. I.: Am. J. Clin. Path. **8**:302, 1938.




PLATE

*(See legend on opposite page)*

COMMENT

Owen [1] attributed the origin of the tumor he described to the metanephric vesicle before the glomerular portion was penetrated by a capillary tuft. He explained its presence in a 52 year old woman on the basis of an embryonic rest which had either been growing slowly for many years or had been quiescent for many years and recently had become activated. Owen proposed the entity of "glomeruloma" of the kidney on the basis of a review of the literature, a consideration of the embryologic aspects and the report of a case.

He offered no proof of the origin or nature of the microscopic tumors in his case but considered them glomerular structures devoid of vascular tufts, apparently because of their rough morphologic resemblance to glomeruli. These neoplastic structures were described as well separated from adjacent tissue by fine fibrous tissue trabeculae and having a peripheral limiting membrane which was lined by a single layer of cuboid cells that exhibited some piling up and some anaplasia. The glomerular structures consisted of masses of cells similar to the lining of the peripheral membrane and were attached to the peripheral lining cells at one or more points. These masses of cells were somewhat anaplastic and varied in size, shape and staining qualities. The cytoplasm was nongranular and had indistinct borders. The nuclei were round, some were hyperchromatic, and an occasional mitotic figure was present. The glomerular units were quite variable in size, but most of them were round and larger than normal glomeruli, although a few were smaller and a few about the same size as normal glomeruli.

From a study of the 8 cases collected from the literature and classified by Owen [1] as instances of "glomeruloma" it appears that there are several different types of tumors represented.

Hildebrand's [2] case resembled Owen's histologically. Structures were described resembling glomeruli but composed of solid masses of epithelial cells with no capillary tufts. Hildebrand considered these structures as derived from an embryonic rest.

In Weigert's [3] case the kidneys showed multiple small tumors, which were reproducing tubular structures and solid masses of cells. He mentioned the presence of "balled-up" tortuous tubules, the so-called pseudoglomeruli seen in infant kidneys, but did not describe definite glomerular structures reproduced by the tumor. Some of the so-called pseudoglomeruli were larger than usual, and these along with the larger tubules he considered as representing abnormally large growths of normal struc-

2. Hildebrand: Arch. f. klin. Chir. **48**:343, 1894.
3. Weigert, C.: Virchows Arch. f. path. Anat. **67**:492, 1876.

EXPLANATION OF PLATE

*A*, glomerulus-like neoplastic structure in carcinoma of the kidney; × 217. *B*, glomerulus-like neoplastic structure in adrenal metastasis of carcinoma of the kidney; × 217. *C*, glomerulus-like neoplastic structure in lymph node metastasis of carcinoma of the kidney; × 217. *D*, glomerulus-like neoplastic structure in a carcinoma of the prostate; × 217. *E*, glomerulus-like neoplastic structure in a fibrosarcoma with cystic degeneration; × 217.

tures. The origin of the tumor was attributed to tubules or the embryonal anlage of tubules. His diagnosis was "adenocarcinoma renum congenitum."

In Sharkey's [4] case no abnormality was apparent grossly in the kidneys, but microscopically these organs displayed widespread proliferation of the epithelial cells of Bowman's capsules and, in some areas, of the adjacent tubules. There was a transition, from flat and cuboidal to columnar epithelium with stratification. In some areas the changes were larger in extent, with loss of the columnar arrangement. He considered this case to be a carcinoma starting at many points in these kidneys.

Abrams' [5] case appeared to be very similar microscopically to Sharkey's. In a few instances the proliferating epithelium completely filled the capsule. In places the growth penetrated the basement membrane and infiltrated the surrounding tissue, and in not a few cases the epithelium of the renal tubules in immediate relationship to glomeruli was replaced by that of the growth. He stated that in lower animals and in the primitive renal tubule in man the epithelial lining consists of a single layer of cells, and thus the increased cellular mass indicated a new formation rather than a congenital one. This was confirmed by the occasional penetration of the basement membrane by the proliferating epithelium. He concluded that this growth was a primary carcinoma of the kidney, arising in the glomeruli, and that it was possibly associated with persistence of the epithelium of the primitive renal tubule.

Weber [6] described cases of intracystic papillary adenoma of the kidney formed of cubic or elongated epithelial-like cells (with large, deeply staining nuclei, like the lining cells of renal tubules) lying on a connective tissue stroma containing blood vessels. He suggested that this kind of tumor is a special type of primary renal neoplasm in which the intracystic papillary tufts represent a rude, giant (neoplastic) attempt of the tumor to imitate glomeruli of normal kidneys and said that similar bodies are found in some instances of papillary adenocarcinoma of the kidney. He offered the designation "glomerular nephroma" for this type of tumor and suggested that as in carcinoma of the liver and adrenal imitating normal liver and adrenal, so in primary papillary adenoma and adenocarcinoma of the renal cortex the neoplasm may imitate the growth of normal renal cortex by producing papillary tufts in cystlike capsules rudely modeled after normal glomeruli.

Turley and Steel [7] described, in their case, multiple miliary nodules composed of glomerulus-like structures which had tufts of branching and anastomosing capillaries and definite connective tissue capsules. The capillaries and capsules were lined by single and double layers of epithelial cells which were cuboid and cylindric. A few of the cells contained mitotic figures. These nodules were considered as neoplastic and as having arisen from glomeruli and not from tubular epithelium or foreign "cell rests."

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4. Sharkey, S. J.: Tr. Path. Soc. London **33**:195, 1882.
5. Abrams, J. H.: J. Path. & Bact. **6**:384, 1899-1900.
6. Weber, F. P.: Internat. Clin. **1**:84, 1917; M. Press **171**:419, 1925.
7. Turley, L. A., and Steel, J.: J. A. M. A. **82**:857, 1924.

The case of Dschu-Yü-Bi [8] was one of multiple nodules in the kidneys, some of which were adenoma with lipoid-containing cells; others were what were termed "intracystic papillomata."

It is generally considered that most tumors of renal epithelium arise from tubules, but that some may arise from glomeruli is conceded as a possibility. While it is difficult to prove that a tumor does not arise from glomerular epithelium or from metanephric tissue, the burden of proof rests with the proponents of a glomerular origin.

That in the cases of Sharkey [4] and Abrams [6] the tumors may have arisen from glomerular epithelium appears possible, but an unusual hyperplasia must be considered, and to designate either of these as a glomeruloma is misleading. This term has an implication of a tumor arising from all the elements of the glomeruli, as well as reproducing all these elements when well differentiated. The capillary tufts were non-neoplastic in these cases.

In the other cases, as in Owen's, there is only the morphologic resemblance to normal glomeruli on which to base a glomerular origin.

No difficulty was encountered in finding glomerulus-like neoplastic structures in a variety of tumors, such as those of the prostate, breast, colon, ovary and other organs (*D* and *E* in the figure). These structures, as well as those described by Owen,[1] are merely features which any well differentiated papillary adenocarcinoma may show.

SUMMARY

From an analysis of the literature and from a study of other cases, as well as of the case presented here, it is concluded that the term "glomeruloma" is not justified as a designation of a renal tumor showing glomerulus-like structures and that these structures are not reproductions of glomeruli but may be found in neoplasms of the prostate, breast, colon, ovary and other organs.

8. Dschu-Yü-Bi: Beitr. z. klin. Chir. **159**:356, 1934.

# Laboratory Methods and Technical Notes

## USE OF SOLID CARBON DIOXIDE (DRY ICE) IN THE PREPARATION OF MUSEUM SPECIMENS

ROLAND E. BIEREN, M.D., BALTIMORE

In search for a satisfactory method of preparing large gross specimens, especially extremities, for permanent mounting in our museum collection, my associates and I have used the one suggested by Bauer.[1] This utilizes solid carbon dioxide (dry ice) to freeze the fresh specimen, which is then cut into sections with a hand saw. The results have been highly gratifying. A somewhat similar method has been in use in the department of anatomy of the school of medicine of the University of Maryland for preparing sections of cadavers, with excellent results.

I find one objection to Bauer's method as described and have sufficiently improved the technic to warrant a report. When the fresh, unpreserved specimen is frozen and sectioned it presents considerable retraction of the skin and subcutaneous tissues after being placed in a fixative. This is overcome by fixing the specimen first, and this modification has the added advantage that the fixed specimen may be kept indefinitely before freezing. We first tried using a gravity flow apparatus to inject the preservative into the vascular bed. This was entirely too time consuming and in addition was rather messy. We now inject the preservative directly into the specimen along the tissue planes, using a 20 cc. syringe and a long 18 gage needle. If the specimen contains a tumor, we also inject the preservative directly into the tumor. Another advantage is that a joint cavity, as that of the knee, can be distended with fluid under pressure to bring out its relations. We have satisfactorily injected the preservative into an entire lower extremity in this manner in less than forty-five minutes. The amount of fluid needed varies from 750 cc. for the lower part of the leg and foot to 2,500 cc. for an entire lower extremity. The minimum optimum time for fixation is three days.

Kaiserling solution 1 is employed for the average specimen. A 4 per cent solution of formaldehyde alone is satisfactory but does not bring out the color. The specimen after it has been sectioned and trimmed is passed through Kaiserling solutions 2 and 3.

We have found an average of 30 pounds (13.6 Kg.) of dry ice per specimen to be sufficient. It is delivered in 3 pound (1.3 Kg.) blocks about an hour before it is to be used. The 3 pound block is most satisfactory for handling; larger blocks are too bulky, and smaller ones evaporate too quickly.

From the Department of Pathology, School of Medicine, University of Maryland.

1. Bauer, J. T.: Arch. Path. **28**:396, 1939.

The specimen is surrounded with the ice in a cardboard container lined with two layers of heavy paper. This is done at 4 p. m. By 9 o'clock the following morning the specimen is ready for sectioning. A power-driven band saw is used to cut and trim the frozen specimen to the desired size and shape. By careful manipulation we have been able to bisect our tumor specimens nicely. Sawing with a hand saw is tedious and apt to damage valuable specimens. The specimen is then thawed out either in water or in the original fixative. The sawdust on the cut

Reticulum cell sarcoma of femur.

surface is carefully washed off. The specimen may be stored in Kaiserling solution 1 or passed through Kaiserling solutions 2 and 3 and permanently mounted.

If an immediate biopsy specimen is required, it is obtained when the specimen is received, through a short lateral incision. This is scarcely noticeable in the cut and trimmed permanent mount and, indeed, can often be eliminated when the sawing is done. Ordinarily, we cut a small waste strip off the frozen specimen for histologic study.

The cost of the dry ice has been 3 cents a pound plus a small service charge for cutting. By accumulating specimens and freezing several at one time, we have reduced our average cost per specimen to between

40 and 50 cents. Considerable economy is possible through properly trimming the fresh specimen. This reduces the amount of Kaiserling solution needed and also the amount of ice.

Some form of refrigerator might be preferred to the cardboard box. If one is used, caution must be taken to leave an escape vent for the evaporating gas, otherwise the box will be wrecked by the accumulated pressure. We prefer the cardboard box because it is portable. This property is necessary since the power saw we have access to is located in another building. Heavy rubber gloves are worn when handling the ice and the frozen specimen. No other precautions have been found necessary.

# A COMBINED STAIN FOR FAT AND ELASTIC TISSUE

CLAUDIA FRENCH, NEW YORK

Studies on experimental atherosclerosis in this department have necessitated the staining of various organs so as to demonstrate simultaneously nuclear structure, fat and elastic tissue. The combined fat and elastic tissue stains described by Herxheimer [1] possess certain disadvantages, such as a tendency to the formation of a precipitate, inconstancy of results and absence of a specific nuclear stain.

With the following method, nuclei, elastic tissue and fat are stained differentially. The stain is applied to frozen sections of tissue fixed in a 4 per cent solution of formaldehyde, preferably after embedding in gelatin. Such embedding reduces distortion and wrinkling to a minimum.

## METHOD OF EMBEDDING

1. Fix tissues in solution of formaldehyde twenty-four hours or longer.
2. Wash in running water five hours.
3. Place in a 5 per cent aqueous solution of gelatin (Knox) at 37 C. for twelve to twenty-four hours.
4. Place in 10 per cent aqueous solution of gelatin at 37 C. for six to twelve hours.
5. Embed in 10 per cent gelatin. Harden in ice box two to four hours.
6. Before cutting, place individual blocks in solution of formaldehyde for twelve to twenty-four hours (either blocks or sections may be preserved indefinitely in solution of formaldehyde).
7. Cut sections on freezing microtome at 10 microns.
8. Before staining, place sections in formaldehyde for twelve to twenty-four hours.

## METHOD OF STAINING

1. Rinse section well in distilled water.
2. Dip several times into 70 per cent alcohol.
3. Place in fat and elastic tissue stain, warmed to not over 45 C., for fifteen minutes. Formula for stain:

| | |
|---|---|
| Weigert's elastic tissue stain (ripened) | 10 cc. |
| Distilled water | 2 cc. |
| Scarlet red, saturated solution in equal parts of acetone and 70 per cent alcohol | 8 cc. |

Mix and filter before use.

4. Rinse in 70 per cent alcohol.
5. Rinse in distilled water.
6. Place in Delafield's (or other) hematoxylin for one to two minutes.

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From the Department of Pathology, College of Physicians and Surgeons, Columbia University.

1. Herxheimer, J.: Technik der pathologisch-histologischen Untersuchungen, Wiesbaden, J. F. Bergmann, 1912, p. 142.

7. Rinse in distilled water.

8. Differentiate in 0.5 per cent acid alcohol if desired.

9. Immerse in weak ammonia until the section becomes blue.

10. Rinse in distilled water.

11. Transfer to a slide, drain and mount in glychrogel.[2] (If desired, 1 per cent aqueous *vert lumière* may be used as a counterstain after the hematoxylin, followed by mild decolorization in 60 per cent alcohol.)

## RESULTS

Fat is orange-red; elastic tissue, purple-black; chromatin, blue; fibrous tissue, green (if *vert lumière* is used).

2. Zwemer, R. L.: Stain Technol. **10**:21, 1935.

# General Reviews

## PROPERTIES OF CANCER CELLS

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ST. LOUIS

A direct attack on the cancer problem is to try to discover the weak points of malignant cells in order that some treatment may be devised which will kill them, or prevent their multiplication, without seriously injuring the other cells of the tissues and organs in which they occur. Accurate data as to the distinctive properties of malignant cells are required, also, as guides to prevention. Until it is learned what the changes are in the transformation of normal cells into malignant ones, workers will be laboring in the dark in their attempts to prevent the changes from taking place.

A committee appointed by the Surgeon General of the United States Public Health Service [1] reports that "attempts to establish fundamental differences between normal and malignant cells of the same tissue type have failed to bring out any striking variation in chemical make-up, enzyme content, metabolism or structure." Voegtlin stated in his discussion of the biochemistry of malignant tissues that "no conclusive evidence exists at present which reveals any qualitative differences in chemical composition between normal and malignant tissues. Whatever differences do exist are of a quantitative nature, the biological significance of which is difficult to evaluate."

### THE COMPARISON

By a "qualitative difference" is usually meant the presence in one of two objects compared of a substance or property absent in the other. If malignant cells differ from normal cells of the same sort by having undergone a somatic mutation or by the possession of a virus, they would differ in this sense. Such a qualitative difference would, however, be really quantitative, because it is the difference between zero quantity and some other quantity.

In general, differences between cells do not involve the presence or absence of something. They are, on the contrary, quantitative and positional differences of substances which occur in both and are widely

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1. S. Bayne-Jones, R. G. Harrison, C. C. Little, J. Northrop and J. B. Murphy (Pub. Health Rep. **53**:2121, 1938).

distributed in living cells. Thus, a difference in the *quantity* of water in two cells of the same size confers a difference in *quality* which is expressed in not one but in many properties.

To limit this comparison between normal and malignant cells to features possessed exclusively by one or the other would be economical both of time and of space, but it would exclude many differences which may not themselves appear to be very significant but which when integrated with each other may nevertheless lead eventually to an understanding of the behavior of malignant cells.

The significance of differences reported in the literature is often difficult to estimate. No single individual is equally competent to estimate the value of chemical, physical, physiologic and pathologic evidence. Confidence in the results increases with directness of the comparison. It is not sufficient that this be between malignant cells and normal cells of the kind which gave rise to them, because neither are uniform in their properties. Both go through periods of youthful vigor, maturity and old age, ending in death. To compare young epidermal cells, capable of multiplication, with keratinizing cells in a squamous cell carcinoma, which have lost this property and are dying, would be misleading. Selection of corresponding periods in the life cycles of both is difficult, but it should be attempted.

The ideal comparison would be between all stages in the lives of cells that have become malignant and all stages in the lives of their normal prototypes, beginning at the stage during which the malignancy arose.

Identification of the stage of onset of malignancy is not always a simple matter. Those who believe that malignant tumors arise not from differentiated cells but from as yet unrecognized embryonal cells scattered about in almost all parts of the body will not be interested in comparing hepatic carcinoma cells with hepatic parenchyma cells, mammary carcinoma cells with cells of the mammary glands and so on; but this is about all that can be done.

The hosts bearing the cells to be compared should likewise be equalized as far as possible. They should be of the same species and sex. Age is also a factor—more important in some cases than in others. It would not do to compare the cells of a carcinoma of the cervix arising during the years of menstrual activity with normal cells of the cervix excised before puberty or after the menopause.

Not only directness of the comparison but also directness of observation is necessary. Microscopic comparisons, in which attention can be focused on the malignant cells, excluding the stroma, are more direct than chemical ones that include the stroma. This is freely admitted, and for chemical analysis tumors with comparatively little stroma are preferred. But it is also difficult to collect normal cells of the same type

for comparative analysis. Their mixture with vascularized connective tissue is just as intimate, and there is the further difficulty that normal cells do not, as a rule, occur in sufficiently large masses.

Malignant cells are seldom uniform in their properties throughout a tumor. The cells in some areas may be proliferating rapidly, while those in others may be undergoing fatty, hydropic or some other variety of degeneration. An experienced pathologist can identify these degenerating parts of a tumor in the gross, and sometimes they can be dissected away from the tissue subjected to analysis. In any case every tumor analyzed should be examined microscopically. Yet reports of chemical analyses frequently show no indication that discrimination was exercised in the collection of material.

Observation is made more direct by the use of tissue cultures. Many helpful comparisons have been reported of sarcomatous cells with cells of the same type from which they arise, but to employ tissue cultures for comparison of carcinomatous cells with their epithelial precursors is seldom feasible. The epithelial precursors are more difficult to cultivate than the mesenchymatous ones. To function normally, and consequently to be structurally normal, they have to be arranged in a definite way, provided with blood vessels, nerves and lymphatics and possessed of facilities for the removal of secretions or excretions. In tissue cultures, cells of any sort, whether normal or malignant, are living under artificial conditions since it is not possible to duplicate their natural tissue fluid environments.

The logical method of presentation would be to take the types of malignant cells one by one and give all established facts in a comparison of each with its normal prototype. This would, however, necessitate repetition time after time of a whole series of properties. Within the limited space available here, more is to be accomplished by listing the properties which have been investigated, making clear the types of malignant cells to which the observations apply. The absence of change must be taken into consideration, as well as its presence, if the comparison is to be constructive.

Limitation of scope is obviously necessary. An attempt is made in this survey to exclude benign tumors, since they are radically different from malignant ones (Reimann and Toennies). Dictates of available space limit the comparison to malignant cells of mammals, though much of value is thereby eliminated. Since it is impossible to give the complete literature on any topic, only the most recent papers are cited. Through them important earlier work can be found.

To decide the best order of presentation is difficult. The cell is the most complex unit known to man. All of its properties are interrelated. Logically, no one of them can be fully discussed without reference to all of the others. If knowledge about one were complete, it would

embrace them all. Perhaps the simplest plan is to select a few of the many properties and to present them in three groups: (1) morphologic, (2) physical and chemical and (3) functional. Of course, such a division is necessarily artificial.

### MORPHOLOGIC PROPERTIES

*Polarity.*—This property is as fundamental to the cytologist as it is to the physicist. It is organization with two opposite poles, as in a magnet. Polarity is more definite in epithelial cells than in mesenchymatous ones, and consequently changes in it are more pronounced in carcinoma than in sarcoma. As epithelial cells cease to cooperate with their neighbors in an orderly and regulated fashion, and their orientation is disturbed, it follows that their polarity, or direction of function, becomes altered. Masson (1922) showed that in certain types of carcinoma of the thyroid the polarity of the secretory cells is reversed; Cowdry (1922), however, found evidence of reversal in some nonmalignant thyroid cells. Ludford (1924) observed that the cytologic changes occurring during keratinization are essentially the same in normal and in malignant cells of mice but that the polarity of the latter, as expressed by the location of the Golgi apparatus and mitochondria, is lost except where the malignant cells limit vascularized stroma. The polarity of melanoepitheliomatous cells is indicated by the position of the centrosomes between the nuclei and the capillary bed (Masson, 1933). Malignant cells that invade tissues singly and in groups look as if they had but little polar organization, certainly less than epithelial cells of embryos, which become polarized very early.

*Nuclei.*—There are numerous statements in the literature that the size of the nuclei in malignant cells is distinctive. Thus, Ehrich (1936 *a* and *b*) reported that in benign tumors there is gradual nuclear hypertrophy but that in most of the cancers of man the increase in size is abrupt, being two or four times that of the nuclei of the cells of origin. Schairer was unable to confirm this observation, but in tar cancers he found a greater variation in nuclear size and a greater number of nuclei with large diameters than in normal epidermis. Moreover, in a careful study of the Flexner-Jobling rat carcinoma Grynfeltt encountered a few large nuclei distributed at random, which in his opinion were of no value in diagnosis or prognosis. Nuclear hypertrophy is one of the commonest changes in unusual conditions; it is not distinctive of malignant cells.

In a summarizing paper MacCarty claimed to have established as a fact that "The nucleolus is much larger in proportion to the size of the nucleus in all malignant cells, regardless of the type or origin of the neoplasm, this difference being great enough to permit easy differentiation from all other cells in the hands of one experienced with fresh tissues." That the nucleolus is larger in some malignant cells than in some nonmalignant ones (von Haam and Alexander and others) none

will deny; but to assert that this holds for all malignant cells regardless of type is to court contradiction. Guttman and Halpern could find no significant quantitative difference in the nucleus-nucleolar ratio in benign and malignant cells. Many others have failed to confirm MacCarty. To attempt to reach a diagnosis of malignancy on the size of the nucleolus alone is both unjustifiable and dangerous.

That certain intranuclear bodies are more numerous in benign and malignant tumors than in normal cells, as reported by Page, Regan and MacCarty and by others, is interesting, but again it is unsafe to generalize. Questionable is their conclusion that "the more malignant the neoplasm, the greater the number of intranuclear bodies."

Nuclear hyperchromatism is manifested by some malignant cells, but it is also shown under a variety of conditions by nonmalignant ones. Investigators are usually content to study this property in hematoxylin and eosin–stained sections, ignoring the fact that there is a microchemical method (the Feulgen reaction) which demonstrates thymonucleic acid with a high degree of accuracy. Cowdry (1928) observed that in sections of tissue cultures the nuclei of sarcomatous cells contain more thymonucleic acid than do the nuclei of normal fibroblasts, but he was unable to find a similar difference between sarcomatous cells and fibroblasts in sections of excised tumors. Employing the same technic, Eckert and Cooper could detect no differences between malignant cells of a squamous cell carcinoma of the cervix and adjacent normal squamous cells.

The nuclei of living malignant and normal fibroblasts in tissue cultures were carefully compared by Lewis (1935). In general, he found the nuclei of malignant fibroblasts larger in proportion to cell size, with "heavier nuclear membranes and larger and more irregular nucleoli." Moreover, "the nuclei of the malignant cells are much more frequently deeply indented on the central side than are those of normal ones."

*Nuclear Division.*—Amitosis is probably overestimated as a method of cell division in tumors, as it has been in normal cells. It is not the main type of nuclear multiplication in any tumor. Amitotic nuclear division is not regularly followed by cell division. Nuclear budding is a phenomenon seen occasionally in both neoplastic and nonneoplastic cells.

Unusual and bizarre forms of mitosis in malignant cells have long attracted the attention of pathologists. It is an education to view the elaborate and beautiful illustrations contributed by Pianese. But today interest in these deformations is waning with increasing realization of their occurrence in nonmalignant cells. Since irradiation of normal cells can produce atypical mitosis (Rezzesi), the frequency of atypical mitosis in tumors that have been irradiated for therapeutic purposes may exceed that before treatment.

It is to be expected that the impairment, and frequently the loss of polarity, of malignant cells will lead eventually to modifications in the polar organization of mitosis, especially when malignant cells are finding it difficult to survive, owing to inadequate blood supply or some other influence. Lewis (1935) suspected "that the exact full complement of chromosomes or an exact multiple thereof is not essential to the continued life of a malignant cell." He regards chromosomal abnormalities as only the manifestation of "a more subtle trouble of the cell." The theory that malignant cells differ from the normal cells from which they arise by a somatic mutation resulting from a nuclear change cannot be proved or disproved by cytologic study, because the genes cannot be seen in the cell types concerned.

The angle of the mitotic spindle was measured by Warren, who wrote: "Whereas in the normal cell apparently a symmetrical spindle is the rule, in the cells of malignant tumors varying degrees of asymmetry are not infrequent" but he says that "these variations are at times apparent rather than real."

*Centrosomes.*—According to Zweibaum, the centrosomes in cultures of malignant macrophages are more distinct than those in normal ones. No detailed and direct comparison has been made of centrosomes in malignant cells and their normal prototypes in sectioned and stained tissues.

The number of centrosomes may be increased in cancer cells as well as in normal cells under unusual conditions. Borrel and LeCount demonstrated that in some carcinomatous cells the centrosomes enlarge to form structures indistinguishable from the so-called "Plimmer's bodies," but it is not safe to conclude that *all* Plimmer's bodies and bird's eye inclusions are of centrosomal origin.

*Golgi Apparatus.*—The position of the Golgi apparatus is a more useful criterion of polarity than that of the centrosome, because it can always be demonstrated in epithelial cells, whereas a centrosome is of less frequent occurrence in nondividing cells. Though the Golgi apparatus has been studied in many malignant and normal cells, no helpful difference has been brought to light. Ludford (1929), who has been a leader in its investigation, stated that it is easier to demonstrate this structure in malignant than in normal cells but gives no clue to the reason for this difference. Bagozzi expressed the opinion that there is no fundamental difference between the Golgi apparatus of the normal and that of the malignant cell, though he reported that the more anaplastic tumor cells are the more striking are the variations in the Golgi apparatus.

*Mitochondria.*—No other microscopically visible cytoplasmic components are so universally present in living cells as are the mitochondria. It is therefore not surprising that they have been repeatedly studied

in the hope of bringing to light some significant difference between malignant cells and their normal prototypes. Table 1 represents a review of comparisons of malignant sarcomatous cells with normal mesenchymatous cells in tissue cultures. It could be made much longer, but it serves the purpose of showing how apparently conflicting are the available data.

In regard to carcinoma, also, there is little uniformity of opinion. That the mitochondria change their properties somewhat from those exhibited by normal cells is to be expected. The alterations are in size, number and distribution, but they are not the same in different tumors, and characterization of the changes by direct comparison with mitochondria in cells of exactly the same sort from which the malignant ones arose has seldom been made. However, Cooper and Seelig by careful

TABLE 1.—*Comparisons of Mitochondria in Malignant Cells with Those in Normal Cells*

| Tumor | Mitochondria | Reference |
|---|---|---|
| Jensen rat sarcoma..... | "Are finer and less refractile than those of normal mesenchyme cells illuminated by the dark ground method" | Fell and Andrews (1927) |
| Same..... | "Are shorter and larger than those of normal fibroblasts" | Carrel and Ebeling (1928b) |
| Same..... | Are "usually smaller" | Ludford (1934a) |
| Crocker rat sarcoma..... | Are "similar to those of normal cells" | Carrel and Ebeling (1928a) |
| Walker sarcoma 1..... | Are "much smaller than those in normal fibroblasts" | Lewis (1927) |
| Rous sarcoma..... | Are more numerous and more filamentous and stain less intensely than those in normal fibroblasts | Zweibaum (1933) |
| Several types of sarcoma | Are usually more numerous and smaller than those in adult fibroblasts | Lewis (1939b) |

studies found that the mean mitochondria-cytoplasmic ratio was slightly greater in normal epidermal cells than in the cells of squamous cell carcinoma. It is likely that other direct comparisons will soon be made, because at least three lines of work appear to focus attention on the mitochondria:

1. Claude has analyzed purified fractions of extracts of chicken embryo and chicken tumor I (a filtrable sarcoma), mouse embryo and mouse sarcoma 180 and 1540. He has found that the purified substances are particulate and closely resemble one another in several ways. His assumption that "the granular elements of the purified tissue fraction may represent isolated mitochondria or fragments of mitochondria" is interesting, because "at least one of these fractions possesses tumor-producing activity." One reason given for the identification is the similarity in size which he found between the granules and the mitochondria. Unfortunately, he accepted for the diameter of mitochondria

a range from 0.2 to 0.05 micron which I mentioned in 1918. This estimate was obviously a mistake, because the smaller granules of this range would be beyond the limit of microscopic resolution with direct light. Moreover, I gave what I believe to be fairly correct estimates in both earlier and later publications and qualified the estimates by explaining that the size of mitochondria is not constant or uniform but varies with cell type and conditions. Claude's granules are definitely smaller than any mitochondria thus far reported. This does not mean that they are not the remains of fragmented mitochondria, but further evidence is necessary on several other points, in addition to size, before one can accept his assumption that the granules are mitochondria.

2. Groffi has reported observing with a fluorescence microscope that carcinogenic agents rapidly penetrate the cytoplasm of both benign and malignant cells in vitro, though they probably do not enter the nuclei. The mitochondria in the cytoplasm showed a selective affinity for the carcinogen, and the author suggests that the carcinogens derange cell metabolism through direct action on the mitochondria. The observation is intriguing, and will have to be checked, but it is not unusual for substances to accumulate on the surface or within mitochondria (Cowdry, 1926). There is as yet no proof that the mitochondrial changes that occur are the direct result of the action on them of the carcinogen. The changes may be brought about by alterations in the cytoplasmic environment of the mitochondria.

3. A. Goerner (1938) claimed observation of a vitamin A–depleting action of a carcinogen on mitochondria, but in a later paper the Goerners (1938) stated that the results "point rather to a chemical combination of the vitamin with some other cytoplasmic constituent." This line of work will be referred to later under "Vitamins."

*Microscopic Peculiarities.*—Many peculiarities have been advanced, but none have been found to be specific for malignant cells. Lipschütz claimed that a so-called "plastin reaction," and that structures referred to as "stegosomata," were characteristic of malignant cells. This was not confirmed by Caccia and Liégeois. Roskin expressed the opinion that malignant cells differ from normal ones in failure to stain with rongalite white. Despite the fact that Lang found that certain normal cells also remain unstained, Roskin still held this method to be effective in the diagnosis of malignant cells. Unpublished studies by Seelig in the Barnard Free Skin and Cancer Hospital lend no support to Roskin's contention.

### PHYSICAL AND CHEMICAL PROPERTIES

*Viscosity.*—Guyer and Claus have reached the following conclusion: "Judging from the lack of displacement of cellular contents in tumor cells subjected to ultracentrifugalization at extremely high speed, the

protoplasm of cancer cells, notably that of carcinomas and adenofibromas, has a decidedly greater viscosity than that of normal tissue cells." They have explained that this "general stiffening" is manifested by the nuclear as well as by the cytoplasmic contents of the cancer cells.

In order to subject the malignant cells to the same centrifugal force as normal cells they implanted bits of Flexner-Jobling carcinoma into the adrenal, kidney, pancreas and other organs in rats, and after growth had taken place they centrifuged the two together. This was, however, not a direct comparison of the malignant cells with their normal prototypes, because the former did not arise in these organs.

Their figure 14 shows marked displacement in a section of adrenal cortex, and figure 15, little or none in a section of a carcinoma implant in the same adrenal, both centrifuged together. Adrenal cortical cells are very rich in lipids, probably more so than the carcinoma cells. Guyer and Claus used an air-driven ultracentrifuge of the Beams type. In my experience there is during such centrifugation a slight rise in temperature. This would tend to lower the viscosity, especially of lipid rich cells.

Employing the technic of microdissection, Chambers and Ludford (1932a) were unable to discover any differences in consistency between the cells of two mammary gland cancers and normal cells in tissue cultures. If, however, a difference does exist, one would expect malignant cells, capable of multiplication and invasion and youthful in some respects, to be less stiff than normal ones of the same types, to have a lower rather than a higher viscosity.

*Water Content.*—Cramer found that all of several tumors examined contained relatively more water than normal tissues and further that their water content varied directly with the growth rate of the particular tumor as measured by the mitotic index. Those with most water grew the fastest. This has been confirmed. The same relation holds to some extent for normal tissues; that is, the tissues of embryos have generally a higher water content and grow faster than those of older individuals. Exceptions were enumerated by Needham, and exceptions may likewise occur for malignant tissues.

These determinations of water content relate to comparatively large and complex masses of tissue, not directly and exclusively to the malignant cells and their normal prototypes. An indirect way of getting sharper localization might be to compare the ice crystals and survival of cells similarly frozen and thawed. The freezing points of normal and neoplastic tissues have been compared by Howard but it was not done on a cellular basis.

*Minerals.*—After careful study Shear reported: "So far as the mineral content of tumors is concerned, young, actively growing tumors appear to be richer in potassium than slowly growing or old tumors;

the reverse appears to be the case with calcium." But a comparison of rapidly and slowly growing normal tissues might show the same thing.

Voegtlin (1937) wrote that "Analytical data *suggest* that certain tumors *apparently* contain less copper than normal tissues. . . ." The italics are mine. This difference, if it exists, is of interest in connection with experiments by Chalkley and Voegtlin which showed that traces of copper powerfully inhibit the nuclear growth rate of Amoeba proteus. Perhaps there is in tumors, as in anemia, a copper-iron relationship.

By microincineration, organic material and certain minerals volatile at a high temperature can be removed from a section, leaving the other mineral salts in approximately the position that they occupied in the cells during life. In normal adult cells there is a fairly definite pattern of mineral distribution for each tissue (Scott).

Olch has reported a finely divided, faintly bluish ash not only in carcinoma of the skin but also in chronic cystic mastitis, hyperkeratoses and warts. Hueper found a similar looking ash in specimens of actively growing tumor tissues and expressed the opinion that the cells in question are not rich in calcium. The chief components of the bluish ash are probably sodium and potassium (Scott). Only a beginning has been made in comparing the minerals of malignant cells with those of their normal prototypes. Olch observed that the epithelial cells of the resting mammary gland contain a lot of calcium and that it is only with proliferation that the aforementioned bluish ash appears, as the white ash of calcium magnesium becomes less apparent. But perhaps the bluish ash remains in about the same amount and is merely unmasked by decrease in the heavy-looking white ash.

According to Policard and Doubrow, the ash of tumors decreases with embryonicity of the growth. And Policard and Pillet expressed the opinion that, in general, proliferating tissue has a low ash content. But it is admitted that there is great variability in the mineral content of the cells within a single tumor (Schultz-Brauns; Hueper); further, that the more degenerated parts contain more calcium and magnesium residue. Hueper expressed the belief that increase in nuclear calcium is the first indication of decreasing vitality of the cells. Horning detected an increase in total minerals in the malignant cells as well as in keratinizing cells of tar tumors. The same observer has reported mineral increase in mouse transplantable carcinoma 27 as soon as six to seven hours after irradiation. The maximum increase is on the sixth day in association with degenerative changes caused by the radiation.

*Lipids, Proteins and Carbohydrates.*—Voegtlin (1937) has reported that, according to a number of workers, malignant tumors appear to be much richer in lipids, especially cholesterol and its esters and phospholipins, than benign tumors and normal tissues. Here one thinks at

once of a possible correlation in malignant cells between lipids and mitochondria, vitamin A and permeability of cell membranes. No marked differences have been demonstrated in the proteins and carbohydrates of malignant and normal cells.

*Vitamins.*—Several vitamins have been studied (Brabec), but only in regard to A is the comparison between certain normal and malignant cells direct enough to be significant.

The Goerners (1938) have reported that they could detect no vitamin A in the tumor cell mitochondria of the Flexner-Jobling rat carcinoma and R-39 sarcoma, though the hepatic mitochondria of animals bearing the tumors contained an abundant store of the vitamin, in fact about as much as those of normal animals.

In a later paper (1939) they made the comparison between malignant and normal cells more direct by producing tumors in the livers of rats and comparing the results of vitamin analyses of the tumors and of the non-neoplastic hepatic tissues about the tumors. Again they found vitamin A absent from the tumors but present in hepatic tissue. It would appear that these tumor cells differ from their normal prototypes in having lost the ability to store vitamin A. That this is due to some change in the mitochondria is not certain. The Goerners have not made parallel cytologic studies of the mitochondria to discover whether there is any microscopically visible change in them coincident with the change in vitamin A content. Dr. C. Carruthers, working in my laboratory, has observed in livers of mice depleted of vitamin A by intraperitoneal injections of a carcinogen that the mitochondria resemble closely those of normal livers containing much of the vitamin (personal communication).

*Enzyme.*—Enzyme analysis shows no fundamental difference (Krebs, Sugiura and co-workers, and many others), but in regard to tissue cultures Fischer reported that cancer cells differ from normal cells by the liberation on disintegration of active proteolytic enzymes which enable them to live in mediums which do not support normal cells. According to Langer (1936-1937), the Ehrlich mouse carcinoma and the Brown-Pearce rabbit carcinoma are more digestible by trypsin and papain than normal organs, whereas pepsin digests normal tissues better than tumors. Raab and Breuer found that human malignant cells are almost entirely destroyed by 0.6 per cent trypsin as compared with normal cells, which are not digested. The described differences may depend partly on differences in relative proportions of digestible substances in complex tissues and organs, not entirely on differences in digestibility of malignant and normal cells of the same type.

## FUNCTIONAL PROPERTIES

*Life Span.*—Carrel (1925) stated that "The malignant monocyte differs from the normal one chiefly because it is a diseased cell which is

short lived." More recently Fischer expressed the same view of the shortness of life of malignant cells. This is interesting in view of the oft repeated statement of Loeb that cancer cells are potentially immortal.

Take the idea of immortality first. Malignant cells will go on multiplying for years if the conditions remain favorable. But so also will certain undifferentiated normal cells. There is no evidence that cancer cells are potentially any more immortal than fibroblasts. In the tissue cultures of Carrel and Ebeling the latter have continued to reproduce themselves far beyond the life span of the chicken from which they were taken. Basal cells of the epidermis continue to multiply as long as life lasts, and one cannot say that their multiplication would not go on for a very long time if favorable conditions were provided.

Cancer cells and undifferentiated normal cells are immortal in the sense that their distinctive vital properties appear again after each multiplication. But the life of the individual normal cell is strictly limited and perhaps that of the malignant cell likewise. Daughter cells resulting from cell division are not the same individuals as the cell that divided. The part is not equal to the whole. Particularly fundamental are the differences that result from asymmetric mitosis, giving an unequal distribution of chromatin, which makes the daughter cells not only different from the parent but also from each other. Normal reduction mitosis, by which the number of chromosomes in the daughter cells is reduced to exactly one half of that of the chromosomes present in the parent sex cell, unless the latter contains an accessory chromosome, also produces cells radically different from the parent.

Returning to the statements of Carrel and Fischer, it is clearly difficult to measure the length of life of individual cells. The period is short for rapidly multiplying malignant and normal cells, since it is their length of life as individuals from one mitotic division to another. Length of individual life may be, and often is, longer when division is halted. The average period between the last cell division and death of the individual resulting from that division can in a few cases be roughly estimated.

Thus, barring injury, individual nerve cells may live a hundred years, individual renal cells for a long time, while the length of others is to be measured in months or weeks. The range of difference in length of life of malignant cells of different types is not so wide. They, by contrast, do not as a rule live for periods of definitely characteristic length during which they discharge some particular function. This segment of their lives appears to be more or less eliminated. Whether the total length of their individual lives is thereby shortened, compared with that of their cells of origin, is the question.

Examination of malignant tumors, in which there is a greater proportion of dividing to nondividing cells than is found in their tissues of

origin, where almost all of the cells are differentiated and serve some special function, certainly gives the impression that the total length of life of malignant cells is shorter than that of their normal prototypes.

But it is not unusual to encounter sections of rapidly growing tumors in which there are astonishingly few mitoses. It is possible that the time consumed by a single mitosis is shorter than in normal tissues, so that the number seen at any one time will be smaller than that expected. It is also possible that there is a mitotic rhythm in tumors and that the tissue may be examined at the point of minimum frequency. Still another possibility is that a considerable number of malignant cells, after ceasing to divide, may not die and be removed quickly, but, instead, may persist in a life of idleness. This is what may happen in the period of latency that tumors occasionally exhibit. How long the individual tumor cells could continue living after their last division if living conditions remained favorable is impossible to predict.

Both malignant and normal cells may die quickly or slowly. When slowly, preliminary signs of degeneration are more noticeable. Tumor cells, according to Ewing (1940), "suffer the same degenerative changes as normal tissue." Overcrowding may result in the death of malignant cells, in which case they die in great numbers *en masse*. In normal tissues cell death is more an individual affair, though the cells may die in orderly strata, as in the epidermis in consequence of progressively increasing deprivation of vital necessities. If central necrosis is regarded as usual or statistically normal for certain tumors, the actual length of life of their individual cells is probably shorter than that of their normal prototypes.

Fischer reported that "even when dead, normal cells and cancer cells behave in different ways; whereas the normal cells remain for a long time among living cells in a rather inert state, the body of the dead cancer cell is readily hydrolysed and soon disappears." This may, however, not be due to any difference in the cells but rather to one in their fluid environments. His observations were made chiefly on tissue cultures. Among the cells that persist longest, though dead, are duct cells of the submaxillary glands of guinea pigs afflicted by the salivary gland virus.

*Special Functions.*—The special functions that constitute the service rendered by most normal cells to their community during large parts of their natural lives are seldom equally discharged by their malignant descendants.

Secretion is a property retained in differing measure by malignant cells. Thus hepatoma produces bile (Strong and Smith); osteogenic sarcoma, phosphatase (Franseen and McLean); thyroid, adrenal cortical and medullary, pancreatic islet and ovarian tumors, to mention only a few, often continue in some measure to manufacture and discharge their

own special hormones. It is significant, as Foulds (1940) has remarked, that malignant cells in endocrine tumors continue in some cases to function, since their only essential need is vascularity.

The formation of melanin is an important function of certain normal cells. Much melanin is found in the malignant cells of black melanoma and little or none in those of amelanotic melanoma. The exact origin of these tumors is disputed; but if they are derived from cells possessing the potency of forming melanin, this function is retained to a marked degree by some malignant cells of this type and is not evidenced by others.

Some epithelial cells discharge their allotted function by dying in the right way—they keratinize. Malignant cells of the same lineage may also keratinize, though perhaps in not quite the same fashion.

The degree of retention of irritability and conduction by nerve cells in ganglion cell tumors has not been studied.

Mesenchymatous cells, like others, learn during development to serve numerous special duties. The contractility of the cells of smooth and striated muscle tumors is unknown. Fibroblasts are concerned in some way with fiber formation—a function that is manifested in different degrees by sarcomas. Motility and phagocytosis will be referred to later.

It is therefore not unusual for malignant cells to retain in some measure the function of the cells from which they were derived. In proportion as they lose this function, their structure departs from type and they are said to be dedifferentiated. Obviously, in estimating the extent of dedifferentiation the starting point is the degree of differentiation, or the stage in the life history of the normal cells at the time the malignant ones were formed from them. In malignant leukemias the extent of dedifferentiation is not to be gaged by comparing the malignant cells with lymphocytes or leukocytes but with less specialized cells, extremely difficult to identify. Basal and squamous cell carcinoma of the skin may not arise from cells of the same age.

Dedifferentiation, or anaplasia, is shown not only by neoplastic cells. In the repair of ciliated epithelium, to cite a single example, there is marked but temporary dedifferentiation (Boling). The difference is that for the malignant cells it is generally permanent. An exception is the progressive differentiation of the cells of squamous cell carcinoma in epithelial pearl formation.

*Organization.*—Reimann stated that cancer cells are unable to organize, that they cannot "organize at all," that they manifest an "entire lack of organizing properties." He and Toennies have defined organization "as that series of processes by which cells of various differentiations gather in integrated groups to form organs and parts which will and do function in the organism."

Yet it is doubtful whether organization is altogether limited to normal cells. In some tumors the malignant cells show a distinct tendency to become arranged in a manner suggestive of the tissue of origin. In the metastases of some endocrine gland tumors the malignant cells become integrated with differentiated stroma cells, blood vessels, and other structures, and the masses so formed may function within the organism in much the same way as the original endocrine organ.

It would be surprising if malignant cells, multiplying autonomously, could maintain as complicated integration as other differentiated cells that are incapable of multiplication. The system would quickly get out of balance.

*Metabolism and Respiration.*—Possible differences between malignant and normal tissues have been considered critically by Voegtlin (1937). In his view ". . . high aerobic glycolysis does not strictly differentiate malignant tumors from normal tissues." He also questioned the claim "that malignant cells derive their energy for growth exclusively from carbohydrates . . ." and cites reports that some normal tissues can proliferate in vitro "under practically anaerobic conditions."

A direct and controlled comparison of aerobic glycolysis of Walker rat sarcoma cells and normal fibroblasts, made in vitro by Victor and Lewis shows a higher rate in the former.

Orr studied changes in $p_H$ revealed by alterations in color of the indicator, phenol red, injected into mice during experimental carcinogenesis. He found indications of a decrease in $p_H$ in the tumors not present in surrounding non-neoplastic epidermis. By the direct injection of indicators into the cytoplasm of mouse carcinoma 27, mouse tar carcinoma 2146, Crocker mouse carcinoma and normal mammary gland cells in tissue cultures, Chambers and Ludford (1932 *b*) found the $p_H$ of all to be between 6.4 and 7.

Carrel and his associates have compared the nutritional needs of several sorts of malignant cells in tissue cultures. Their summarized results (Carrel 1929, 1932) indicate that the malignant cells studied differ from normal cells of the same type in their ability "to use substances which do not support normal cell proliferation" through "an increased production of proteolytic ferments and of acid." Fischer has already been quoted on this point. Lewis (1939 *f*) has found that "cultures of malignant cells tend to liquify plasma clots much more than normal ones."

Kögl and Erxleben have presented evidence to show that malignant cells differ fundamentally from healthy cells by not discriminating in the incorporation of natural and unnatural amino acids; that is, they take in both *l* and *d* forms while normal cells utilize only the former. From their critical examination of evidence Dodds and Dickens have expressed

the opinion that, though no final conclusion can be reached, the specificity of this difference is to be questioned, owing to work by Chibnall and his associates.

*Permeability.*—Whether the intake of substances by malignant cells differs from that of normal cells of the same type is an important question. Shear's (1935) work on the swelling of normal and malignant cells of mice in vitro did not seem to provide an answer, for he stated: "While tumor cells appeared to swell more rapidly and to a greater extent than normal cells, no definite conclusion was drawn in this matter because of the variability in the results."

It is convenient to use substances that can be recognized microscopically after they have entered the cells. Consequently, many experiments have been made with so-called vital stains, which consist of fine particles in suspension. Ludford has led in comparing the ability of malignant and normal cells to take in and segregate in their cytoplasm trypan blue and similar dyes in microscopically visible masses. He first injected trypan blue into mice bearing a carefully selected series of sarcomatous and carcinomatous tumors. The stroma cells stained, and a few dead malignant cells also, but most malignant cells differed sharply from their normal prototypes by failure to stain (Ludford, 1929). To check the possibility that the difference might arise because the malignant cells do not receive as much dye in vivo as the nonmalignant ones, he later (1932) compared the two under conditions of equal exposure to the dye in tissue cultures, with the same result.

Several possible explanations have been offered by Ludford for this marked difference, including the hypothesis that the cell membranes of the malignant cells may be impermeable to the dyes (it would be better to say less permeable). He also stated that the difference may be "related to some peculiarity of the metabolism of the cancer cell, or of its colloidal state."

The difference is rendered more significant by Duran-Reynals' observation that when poorly diffusible dyes and some foreign proteins are injected intravenously into mice, rabbits and chickens bearing transplantable and spontaneous tumors, the substances localize selectively within the tumors, where they are found in the stroma and not in the cancer cells. This indicates that the permeability of the capillaries in the malignant tissues is greater than that of the capillaries of normal tissues, which may partly compensate for low tumor vascularity, so that the active malignant cells are adequately exposed to the substances.

Ludford (1934 *d*) reported that when the fat-soluble and water-insoluble colored compounds of sudan III and sudan black are applied to normal and malignant Crocker mouse sarcoma cells in tissue cultures, they penetrate into malignant cells "probably to a greater extent than they do into normal cells," though the malignant cells appear to be

less permeable to "water-soluble" compounds like trypan blue. "This behavior is consistent with the view that the plasma membranes of most malignant cells have a relatively greater fat content than normal cells (Ludford, 1934)."

The intake of particles of stain has been likened to phagocytosis. There are numerous reports that malignant cells are able to phagocytose other malignant cells (Graham). Phagocytosis is more common by malignant fibroblasts than by normal fibroblasts in tissue cultures (Lewis, 1927). Barnes and Furth have found that the malignant cells in a transmissible strain of leukemia of mice do not phagocytose tubercle bacilli or carbon particles. From the distribution of neutral red granules in these malignant cells they appear to be related to monocytes. If they are of monocytic origin, this would seem to be an example of loss of phagocytic ability with assumption of malignancy. It sometimes is the other way as with carcinoma.

"Pinocytosis" is a term introduced by Lewis (1931) to indicate drinking by cells in contrast to phagocytosis, or eating by cells. He explained (1937) that he means microscopically visible drinking, not submicroscopic "sipping," which Meltzer termed potocytosis. By this process in tissue cultures "complex fluids of culture media containing proteins and other substances which cannot diffuse into cells are engulfed by the wavy ruffle pseudopodia." When the globules of fluid are first taken in they are, according to Lewis, entirely enclosed by the surface membrane of the cells which invests them. This later disappears as the fluid becomes a part of the cytoplasm.

Macrophages as seen in tissue cultures exhibit the property of pinocytosis better than any other variety of cells, and this probably occurs also in vivo. Malignant sarcoma cells of the rat and mouse also show active pinocytosis in tissue cultures. The process in them is "similar" to that in normal macrophages (Lewis, 1937). The same author reported (1931) pinocytosis in carcinoma cells of the rat. A comparison with the cells of origin of the carcinoma was not made; but it is unlikely that, being epithelial and sessile, they exhibit ruffle pseudopodia. Since Lewis stated that only cells with ruffle pseudopodia show pinocytosis, the malignant cells in this case probably differ from their cells of origin in having acquired the property of pinocytosis.

Malignant cells that do pinocytose needed fluids, which cannot diffuse through their cell membranes, may also take in other fluids, perhaps harmful ones, more readily than other cells, incapable of pinocytosis. If this proves to be the case, those tumors in which the malignant cells resemble macrophages may possibly be especially vulnerable to certain fluids.

The use of substances made radioactive by a cyclotron, and therefore recognizable, will probably afford a new opportunity for comparing

the intake by malignant and normal cells when they are present in fairly large groups. Already Lasnitzki has observed that Jensen rat sarcoma cells do not concentrate radioactive potassium. The significant point for the present comparison is whether the cells of origin of this sarcoma do or do not. The use of radioactive indicators has been described by Hevesy. As will be mentioned later, a few neoplasms concentrate viruses more conspicuously than some normal tissues; but in their case other factors, besides permeability, are probably involved because some viruses are of very large molecular size.

*Motility.*—Zweibaum has concluded that sarcomatous macrophages are characterized by much more motility than normal ones; but this conclusion is based on visual impression, not on direct measurements. To arrange a marathon between malignant and normal cells, with fairness to both, is practically impossible. The only way is to measure the rate of movements that individual cells happen to make by analysis of moving pictures. Lewis (1939 *g*) has found that malignant sarcomatous cells possess a superficial contractile plasmagel layer like normal macrophages.

Ability to move probably depends to some extent on the stickiness of cell membranes. Epithelial cells that grow in sheets naturally stick together, whereas fibroblasts are more solitary. Increase in stickiness is manifested by the adhesion of leukocytes in the blood stream to the walls of injured vascular endothelial cells and by the cohesion of fibroblasts in tissue cultures treated with methylcholanthrene (Earle and Voegtlin). Decrease in stickiness has been described as a factor in the release of maturing blood cells from the bone marrow (Key).

Malignant cells arising in the stratum spinosum of the epidermis cannot break away and invade the deeper tissues until the typically firm connections with their neighbors are loosened. In benign epithelial tumors the cells stick together in arrangements resembling normal cell aggregates; with increase in malignancy, they relinquish this property more and more and strike out for themselves. Perhaps decrease in stickiness of carcinomatous cells is a necessary prelude to their invasiveness.

*Invasiveness.*—It is doubtful whether invasiveness is a property peculiar to malignant cells. If the term simply means penetration of the cells into a foreign tissue—one in which they did not originate—invasiveness is shown by many types of normal cells.

Neutrophil leukocytes, which are too old and highly differentiated to undergo a malignant change, are the most effective invaders. Monocytes and macrophages can also do so, likewise the sarcomatous cells that may arise from them. However, in many, if not in all, cases, invasion by the aforementioned normal cells is in response to a change in the tissue invaded. There is no evidence of the existence of a similar reason

for invasion by sarcomatous cells. The impelling factor or factors for them are not clear. It may be movement in the direction of a more adequate food supply.

The epithelial cells of the fetal chorion normally invade maternal tissues. Ewing (1940) writes that "all the known features of a malignant neoplasm are exhibited by the normal chorion, even the destructive invasion and cachexia." He adds that "the process is not a tumor because of its purpose which shows that it is under the control of organization." But he admits that "the evidence that malignant chorioma may develop from emboli of normal chorionic cells is practically conclusive (Marchand; Pick)." One wonders whether these cells of the fetal chorion are normally malignant and whether this finds expression only in accidental emboli because normally their existence is limited by expulsion of the placenta.

Most types of epithelial cells are sessile, and as long as they remain normal, their invasiveness is nil. The carcinomatous cells to which they give rise therefore differ from them sharply and fundamentally. Perhaps their means of invasion differs from that of sarcomatous cells whose prototypes could invade to begin with, but again there is no evidence. The invasion and destruction of a pure culture of normal fibroblasts by a pure culture of Walker mammary gland carcinoma no. 256 malignant cells has been observed by Earle (1937).

*Destructiveness.*—Much is made of the peculiar destructiveness of cancer cells that invade previously normal tissues. It is different from that of invading macrophages and neutrophil leukocytes, which do not as a rule harm other cells living in the same body unless they have been injured, in which case they may engulf them by phagocytosis, or, if they are too large, invade their cytoplasm and digest them. The phagocytic properties of malignant cells have been mentioned. They play a minor role, if any, in the destruction of living normal cells.

Some think that the normal cells die as a result of pressure exercised by the increasing numbers of malignant cells. Except in special locations, where displacement to provide room for more cells is restricted, the pressure would appear to be but slight. Normal cells and invading malignant ones would be equally exposed to it. If it is really lethal only for the former; the latter must be more resistant to pressure.

According to Voegtlin (1938) "It is conceivable that the excessive amounts of lactic acid present in tumors with the consequent decrease in $p_H$ may be . . . concerned in the destructive action of tumor cells on adjoining normal tissue." Obviously, the destruction may result not only from greater susceptibility of normal cells to acid but also from their failure to compete successfully on equal terms for vital necessities. Any initial advantage of the malignant cells may be increased by their

rapid multiplication in number, whereas the particular normal tissue invaded may not be growing.

*Growth.*—Growth of malignant tumors is sometimes very rapid, but it has been frequently pointed out that few tumors grow as rapidly as does the fetus in utero. And none as quickly as an early embryo. One factor in the growth of tumors is that an increasing number of cells continue to multiply. This does not happen in adult tissues, where dividing cells soon differentiate and lose the power of multiplication, so that the relative number of dividing to nondividing cells is usually smaller than in a rapidly growing tumor.

The idea that malignant cells necessarily multiply more rapidly than normal ones is fallacious. They do sometimes—for instance, in active areas of a basal cell carcinoma as compared with the basal cells of normal epidermis; yet during the years of reproductive activity the frequency of mitosis per cell among the spermatogonia of the testicle far exceeds that in any tumor. And, furthermore, some malignant cells may multiply slowly, so that the tumor appears to be dormant.

How the time required for malignant cells to divide compares with that for normal cells of exactly the same type is not known, but it could be determined from moving pictures like those made by Carrel, Canti, Lewis, and others.

Some sorts of normal cells divide rhythmically, with the peak of maximum frequency of mitosis by night and the minimum by day (Cooper and Schiff; Cooper). Whether corresponding malignant cells exhibit rhythms remains to be determined by direct comparison. Variations in the rate of growth of certain individual tumors do occur, periods of activity being followed by standstill and occasionally by regression.

To imply a difference by speaking of the uncontrolled growth of a malignant tumor and of the controlled growth of normal tissue is unjustfied, for both are controlled. Indeed, the particular rate of growth of a tumor is as much one of its properties as the special rate of growth of any normal tissue is one of its characteristics.

Murphy's working hypothesis is that the rate of growth is the resultant of stimulation and inhibition. He and his associates have described the isolation of an inhibiting factor from certain normal tissues which retards or prevents the growth of mammalian carcinoma, though it is harmless to normal cells. He has also isolated simulating factors. A more direct comparison of the influences of both on malignant cells and their normal prototypes is needed.

The regulation of growth, as far as cellular multiplication is concerned, is not centered in malignant and normal cells in quite the same way. It is essentially endogenous in the malignant cells and partly exogenous and partly endogenous in the normal ones. Increase in

number of malignant cells is more autonomous and dependent on themselves, while that of normal cells is more influenced by the tissue fluids about them. Earle (1937) has reported the stimulating effect of tumor extracts on the multiplication of the same tumor cells and its absence of influence on fibroblasts.

An adequate supply of suitable materials to build up more protoplasm and physical ability of the cells to multiply are prerequisites to growth. If malignant cells are less discriminating in their dietary needs and, being in some respects less differentiated, are physically better able to divide (because of higher water content, for example), the influence on them and on normal cells of the same stimulating and inhibiting factors in like amounts may be quite different.

Growth of any mass of cells depends on mortality rate as well as on reproductive rate. Only when the mortality rate is constant is the "mitotic index" a reliable criterion of growth. If the life of individual malignant cells is actually shorter than that of normal cells of the same sort, it is evident that cellular mortality will operate against growth of a tumor more than against that of normal tissues, which would make the growth of tumors more dependent on multiplication of cells. Increase in volume by heaping up of nonvital components (fibers, tissue fluid, fat) is not an important differential factor.

The continued rapid growth of a malignant tumor while the body becomes more and more emaciated is significant. It points to a difference in the nutritional needs of malignant as compared with normal cells, but there is no reason to suppose that this is the only factor involved. Earle (1939) has emphasized the complete absence of growth of normal mammary gland epithelial cells in tissue culture mediums in which Walker rat mammary gland carcinoma cells grow luxuriantly. This sharp difference between the two may be due to greater adaptability of the malignant cells in the face of changed conditions. Perhaps they do not need an endocrine growth stimulus required by the normal cells.

*Adaptability.*—Measured in some ways, malignant cells seem to be more adaptable than normal cells. This is to be expected if they are really more youthful and less fixed in their ways. Greater adaptability suggests greater resistance but not necessarily. Direct comparisons of malignant and corresponding normal cells in point of adaptability have not been discovered in the literature.

Some evidence has been presented that all the tissue fluid environments within the body are not uniform in their properties (Cowdry, 1939). Malignant cells can metastasize to many such environments from their site of origin and still go on multiplying, often with increased vigor. But these secondary environments are not always those first encountered in the course of the lymphatic or vascular streams. The morphologic character of such malignant cells, as well as that of the

primary tumor cells, may be changed. According to Ewing, a spindle shape is favored by relief from pressure, rapid growth and inflammation. Foulds (1937) described a transplantable carcinoma of a fowl which where the cells were separated by intercellular matrix exhibited spindle-shaped cells, like a sarcoma. Whether normal cells of the same kind moved to different tissue fluid environments would be equally adaptable is an open question.

But the transplantability of some malignant cells is definitely greater than that of normal cells. That they will grow when transferred from one mouse to another of the same genetically pure strain of mice, though normal cells will not survive transplantation from human to human subject, as in skin grafting, does not itself indicate a fundamental difference, because these mice in their similarity approach identical twins and exceed persons belonging to the same blood group. Growth of rat and rabbit tumors in the chorioallantoic membranes of chicks (Schrek and Avery) involves change from one class of animals to another, but in embryonic life this fluid environment is relatively unspecialized and the normal prototypes of the malignant cells might well grow in it likewise. However, many mammalian tumor cells can be transplanted into animals of the same species but not of the same "genetically pure" strain, while the normal cells of mammals cannot. Transplantation of the Ehrlich-Putnoky mouse tumor into rats has been described (Putnoky; Selbie), but the growth is short lived, and the cells can be continued in rats only by frequent transfer at short intervals.

It is customary to refer to some transplantable tumors as particularly "well established." This implies that by continued passage they become adapted to the recipients. In a thorough study of 17 different kinds of sarcomatous cells, extending over several years, Lewis (1935-1936) could find in tissue cultures no evidence of change in the malignant cells since his observations had begun. The question is whether the remarkable changes reported in some of the tumors beforehand were in these malignant cells themselves or in other cells accompanying them. It is possible that in the repeated transplantations of a given tumor the most adaptable type of cells survives—in other words, that there is a weeding-out process. Tumors, especially primary ones, may contain two, even more, types of malignant cells mixed together with stroma cells. One explanation of the formation of a neurotropic virus by many passages of an originally pantropic virus through brains is that the particles having affinity for other tissues become reduced in relative number while the neurotropic ones multiply and dominate.

Strong has observed a gradual change during repeated transplantation of spontaneous tumors in genetically controlled mice. At first they would grow only in the mouse strain of origin, but later they became able to

grow in practically all mice. The reverse, increasing specificity in the requirements of tumor cells, was never observed by him.

The malignant transformation itself is said to be irreversible, but can one be positive that no cells in a tumor population of billions ever undergo an adaptation in the direction of normality? If they did, the chances of their survival might be almost negligible. In the extremely rare cases in which malignant tumors, not of congenital origin, regress, no evidence of such reversion to normality has been reported. On the contrary, the regression appears to be due to death of the malignant cells, occasioned to some extent by activity of the stroma, including lymphocytes.

Spontaneous regression of congenital malignant tumors is less rare, particularly for certain types, as Wells has pointed out in his review. He has emphasized a case, reported by Cushing and Wolbach, of a typically malignant neuroblastoma, observed in a 2 year old boy, which ten years later had completely differentiated into ganglion, capsular and neurilemma cells. This is a demonstration, in his opinion, "that neuroblastomatous cells, even when malignant in character, may go on to differentiate into mature types of cells of nonmalignant character." Other somewhat similar cases appear to support this conclusion; but to check the possibility that such tumors when clinically malignant may have contained some nonmalignant cells of the same type, that regression may have resulted from death of the former and that the differentiated cells found later may have developed from the latter, is beyond the limits of use of present cytologic methods.

The fixity in the behavior patterns of different types of malignant cells through countless mitoses is certainly one of their outstanding features. Granted, however, the continuation of favorable conditions, there is reason to think that some undifferentiated normal cells can keep on multiplying just as long as the malignant ones. The basic difference is that the same behavior is manifested by most, if not by all, the living and vigorous descendants of the malignant cells and only by a small band made up of part of the offspring of the normal cells, which remains behind, retains its fixity of behavior pattern and does not differentiate. The basal cells of the normal epidermis illustrate the phenomenon.

A further comparison of these basal cells with malignant epidermal cells shows other significant differences. They are quite uniform in their properties, while attention has already been called to the wide range of variation in the cytoplasm of malignant cells. Many reports show that malignant epidermal cells are not exceptional in this respect, but occasionally their cytoplasm is remarkably uniform. The variations occur in the mitochondria, Golgi apparatus—in fact, in all of the cytoplasmic components subjected to microscopic study.

The nuclei of the normal basal cells are fairly uniform in size and structure, and mitotic division is regular, so that hereditary properties

resident in the chromatin are equally distributed to the daughter cells. The nuclei of the malignant cells, on the contrary, vary a good deal in size and intensity of staining reaction. Irregular mitoses are not infrequent. The resulting daughter cells, if they survive, will not be governed by the same nuclear hereditary endowments.

Though part of this diversity in the malignant cells may be due to the inclusion of some cells which are not capable of division, it is nevertheless in sharp contrast with the fixity of their behavior pattern. The few available facts suggest that the distinctive behavior of malignant cells as compared with normal cells of the same sort is conditioned by some unseen and unknown influence that acts with great regularity and uniformity within them.

*Susceptibility.*—This is often, but not always, the reverse of adaptability. Cells which cannot adapt themselves to change are, compared with those which can, more susceptible to it. Many efforts have been made to discover the weak points of malignant cells. Their responses to heat (Overgaard; Walker; Johnson), cold (Mider and Morton), poisons (Ludford, 1936), heavy water (Barbour and Allen), light (Taussig, Cooper and Seelig)—to almost every known influence—have been studied. Extraneous factors affecting the development of tar tumors have been reviewed by Seelig and Cooper. Limitations of space permit only brief reference to radiation, viruses and hypersensitiveness.

For malignant as for normal cells, the radiosensitivity differs with the type. Moppett reported that the cells of mouse sarcoma S 37 are *more* radioresistant than normal fibroblasts, both in vitro. Yet Crabtree and Cramer stated that there is nothing peculiar in the make-up of the cancer cell which renders it specifically more vulnerable to radiation than normal cells. The susceptibility is, they believe, not fixed but varies with the environment. Yet, according to Seelig, Eckert and Cooper, "radiosensitivity seems to be an inherent quality of the cell which varies even in individuals of the same species and is not altered by vascular compromise." These observers worked with non-neoplastic epidermal cells. Lawrence, Aebersold and Lawrence have compared the effects of neutrons and roentgen rays on normal and neoplastic tissue, but it is not clear that the cells were of the same type.

The ease with which some viruses grow in malignant cells has excited comment, though this action is not surprising in view of the youthful properties of such cells. Examples are given in table 2

However, the experiments were not performed with the idea of comparing the susceptibility of malignant cells to the viruses with that of their normal prototypes. No mention is made that the latter similarly attracted the viruses. In some cases the viruses were injected directly into the tumors, so that normal cells of the same type did not

have an equal chance to become infected. To infect normal cells is not so easy anyway unless a path is opened for the viruses by a previous injury to them, even so slight as that occasioned by plunging a hypodermic needle into the tissue. Moreover, the normal cells of origin occur in smaller masses than the tumor cells, and the biologic analysis of them in bulk for viruses is consequently more difficult.

The statement by Levaditi and Schoen (1937) that tumor growth is affected only in animals susceptible to the localizing virus—as mice are to the fowlpox virus, while rabbits are not—is important; for, if this holds in other instances, the inhibition of malignant tumors by viruses will be somewhat hazardous. Papilloma virus is said to exaggerate the growth of tar warts in rabbits, with the production in same cases of squamous cell carcinoma (Rous and Kidd; Ahlström and Andrewes).

The literature on immunity to transplantable tumors has been critically discussed by Woglom. It is known that soon after regression

TABLE 2.—*Viruses and the Tumors in Which They May Grow*

| Virus | Tumor | Reference |
|---|---|---|
| Vaccine virus..... | Mouse carcinoma but not mouse sarcoma | Levaditi and Nicolau (1923) |
| Vaccine virus..... | Shope rabbit papilloma cells injured..... | Levaditi and Schoen (1936) |
| Vaccine virus..... | Brown-Pearce rabbit carcinoma..... | Rivers and Pearce (1925) |
| Virus III..... | Brown-Pearce rabbit carcinoma..... | Rivers and Pearce (1925) |
| Rabies..... | Shope rabbit papilloma..... | Schoen (1938 a) |
| Fowlpox..... | Sarcoma 180 and carcinoma 63 and 2,146 cells of mice killed | Haber and Coquoin (1937) |
| Fowlpox..... | Brown-Pearce rabbit carcinoma..... | Levaditi and Schoen (1937) |
| Lymphogranuloma | Ehrlich mouse sarcoma..... | Schoen (1938 a and b) |

of implanted Jensen rat sarcoma the rat concerned is immune to a second implantation of the same tumor, and other instances of the same phenomenon could be given. Ewing (1940) has emphasized the fact that "complete resistance to implantation of a virulent sarcoma may exist in animals bearing an actively growing tumor of the same sort." Malignant cells are like normal cells in that some production of antibody can be brought about by their injection. To quote Ewing again, the "serological evidence points to a form of immunity characterized by local and general hypersensitiveness produced in the immunized animals by absorption of regressing or inoculated tumor tissue."

## SUMMARY

The types of malignant cells probably outnumber those of the normal cells from which they arise. To add together what are thought to be the outstanding features of all of them and to construct a synthetic picture of what *the cancer cell* is like would be both unjustifiable and misleading. It would be as pernicious as the habit which cytologists had until recently

of describing and illustrating *the typical animal cell,* in which they included all that they considered fundamental.

But it is proper to list a few of the many features which have been reported more or less frequently and in varying degrees when a large variety of malignant cells has been examined, notwithstanding the fact that few, if any, of them may be foreign to all normal cells and to non-neoplastic pathologic cells:

1. A loosing or lack of polarity
2. A wide range in variation of nuclear and cytoplasmic structure
3. A decrease in structural differentiation and dependent specific functional activity, except in congenitally malignant cells which are not differentiated to begin with.
4. A decrease in dependence on oxygen supply
5. A decrease in organismal control over cell division and an increase in autonomy, or self regulation, of cell division
6. An increase in transplantability into other individuals of the same species
7. An increase in invasiveness and ability to outlive cells of invaded tissue

At present there is no reliable basis on which to reach a decision as to whether, apart from all the others, a single cell observed in a section of suspected tissue is or is not malignant. When more cells are examined and other features of the tissue are taken into consideration, an opinion may be offered; but even then in some cases diagnosis must await the study of clinical data. If many technics could be applied to the same single cell in question, there might still be reasonable doubt as to its malignancy. The point is that malignancy is a functional attribute. Though structure and function are inseparable, very minute deviations in structure, undetectable microscopically, may condition marked differences in behavior. There is no satisfactory evidence that malignant cells of man possess anything, virus or otherwise, which is wholly absent in normal cells.

The impression gained by this survey of the contrasting properties of malignant and normal cells of the same sorts is that there are a host of cell constituents which differ quantitatively and positionally. The latter difference is very important, because, by different associations, interactions and linkages, of substances in the same quantity marked differences in vital phenomena are created. It is the *tout ensemble,* different but more or less fixed for every type of malignant cell, that counts.

In this quest for differences between malignant and normal cells, many similarities are encountered. These are naturally much more

numerous, because both are vital units which multiply, live their respective lives and die. A few, however, may be mentioned.

1. Both may be classified into many types that breed true.

2. With increase in differentiation there is usually a decrease in cell division and vice versa.

3. Decrease in water content is often accompanied by decrease in cell division and vice versa.

4. In the undifferentiated state, given favorable conditions, both can apparently continue multiplying indefinitely.

5. Motility and invasiveness may be highly developed in both.

6. Both may be invaded by viruses, which increase in amount intracellularly.

7. Both may exhibit similar degenerative changes.

Progress has been slow and irregular, owing to a rather general failure to appreciate the fact that even the comparison of a single sort of malignant cell with its normal prototype is a major problem in which a single investigator can make but little headway. The integrated labor of several specialists over a considerable period of time is required, for the value of the comparison increases with the number of properties compared and the degree of quantitative accuracy of the methods. Much can be done by systematic use of technics now available, of which the following are among those that hold promise of usefulness: microincineration, spectrographic and polarographic analysis, ultracentrifugation, roentgen ray diffraction determinations and the behavior of substances made radioactive by a cyclotron. But new chemical and physical methods that can also be applied to very small pieces of tissue are sorely needed.

Unless the material to be studied is wisely selected, the best technic will be more or less useless. The neoplasms that can be produced with considerable regularity in genetically pure strains of mice by sharply localized application of a chemically pure carcinogen are of suitable size and provide excellent opportunities for detailed comparison of malignant cells, perhaps indeed of cells becoming malignant, with their normal prototypes.

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# Notes and News

**University News, Promotions, Resignations and Appointments.**—Carl V. Weller, Ann Arbor, Mich., has been appointed editor-in-chief of *The American Journal of Pathology* to succeed F. B. Mallory, who has retired.

John E. Gordon, professor of preventive medicine and epidemiology in the Harvard Medical School, has been appointed to succeed the late Hans Zinsser as Charles Wilder professor of bacteriology and immunology.

Angel H. Roffo has been appointed the incumbent of the new chair of "cancerology" of the faculty of medicine of the University of Buenos Aires.

In the medical school of the University of Minnesota, Halvor O. Halvorson has been promoted to a professorship of bacteriology.

**Society News.**—The one hundred and seventh meeting of the American Association for the Advancement of Science will be held in Philadelphia from December 27 to January 2, inclusive.

**Unit of Gerontology.**—The National Institute of Health, United States Public Health Service, is organizing a unit for research into the problems of aging. A survey will be made of the present trends of investigation in this country in the field of aging, and inquiries are being sent to scientists in the basic biologic sciences as well as to clinical investigators. From the clinical point of view the greatest concern is with studies dealing with health evaluation, with mensuration of functional capacity (including criteria of "physiologic age") and with the diseases whose incidence increases sharply in later life (the so-called "degenerative disorders"). It is hoped that the information elicited will promote closer cooperation on the part of investigators in related fields, especially when widely divergent disciplines are applied. The survey will bring out the need for augmented support for significant studies. Information concerning subjects under investigation and the methods of approach is solicited. Letters should be addressed to Dr. Edward J. Stieglitz, Investigations in Gerontology, National Institute of Health, Bethesda, Md.

**Microfilm Service.**—A microfilm service is conducted by the Army Medical Museum on a nonprofit basis for making the resources of the library available to students and investigators who are unable to consult them in person. Address the Microfilm Service, Army Medical Library, Seventh Street and Independence Avenue, S. W., Washington, D. C.

**New Cancer Journal.**—The new journal *Cancer Research* is sponsored by the American Association for Cancer Research, the Anna Fuller Fund, the International Cancer Research Foundation and the Jane Coffin Childs Memorial Fund for Medical Research. The conduct of the journal will be in the hands of an advisory board consisting of the chairman of the editorial committee (James B. Murphy), representatives of the contributing funds, as editorial committee (S. Bayne-Jones, secretary) and a business manager. It is planned to issue the first number in January 1941. Manuscripts should be sent to the secretary of the editorial committee, 333 Cedar Street, New Haven, Conn., and subscriptions will be received by the business manager, A. Vaughn Winchell, American Oncologic Hospital, Thirty-Third Street and Powelton Avenue, Philadelphia. One volume of twelve numbers will be issued each year. The subscription price is $5 to members of the American Association for Cancer Research and $7 to nonmembers.

# Abstracts from Current Literature

To Save Space the Original Titles of Abstacted Articles Sometimes Are Shortened

## Experimental Pathology and Pathologic Physiology

Mechanism of Leukocytosis with Inflammation. V. Menkin, Am. J. Path. **16**:13, 1940.

Leukotaxine, a crystalline nitrogenous substance recovered from inflammatory exudates and known to increase capillary permeability and cause diapedesis of polymorphonuclear leukocytes, fails to induce an increase in the leukocytic level of the circulation in either the dog or the rabbit. Hence it can scarcely be responsible for the leukocytosis of inflammation. There is present in exudates a leukocytosis-promoting factor capable of inducing a rise in the leukocyte level of the dog. This is demonstrable when either the whole or the cell-free exudate is introduced into the circulating blood. An inflammatory exudate removed from an animal with leukopenia and injected into the normal dog fails, as a rule, to induce a marked rise in the leukocyte count. Blood serum, sterile broth, bacterial cultures of exudates and cultures of killed bacteria (Staphylococcus aureus) are all ineffective in causing an increase in the leukocyte level of the circulation. Histamine and adenosine are likewise essentially inactive. Extraction of exudates containing the active leukocytosis-promoting factor for histamine yields an end product incapable of inducing leukocytosis. Nucleic acid injected into the blood stream in high concentration favors, after a considerable latent period, a rise in the number of leukocytes. This delayed effect differs from the prompt response induced by exudates. The action of the leukocytosis-promoting factor seems to be primarily on the bone marrow, producing an outpouring of immature granulocytes into the circulation. The factor is thermolabile. Heating the exudate to 60 C. inactivates the material. The factor is found after prolonged dialysis of the exudate through a cellophane membrane to be in large part indiffusible. Further studies are now in progress in an endeavor to identify the nature of the leukocytosis-promoting factor present in inflammatory exudate.

From Author's Summary.

Experimental Production of Cirrhosis of the Liver by a Deficient Diet. A. R. Rich and J. D. Hamilton, Bull. Johns Hopkins Hosp. **66**:185, 1940.

Cirrhosis of the liver, of a type resembling Laennec's cirrhosis in man, occurred in all of 14 rabbits kept for twenty-five to one hundred and thirteen days on diets supplemented by various vitamins but lacking yeast. The present evidence indicates that the cirrhosis was due to the lack of some factor contained in yeast but different from vitamins $B_1$, $B_2$, $B_6$ and nicotinic acid. Ascites occurred in 7 of the animals. Microscopic formed gallstones developed in the intrahepatic bile ducts in 2 animals.

From Authors' Summary.

Protein Consumption and the Restoration of Lost Organ Tissue. T. Addis and W. Lew, J. Exper. Med. **71**:563, 1940.

At all levels of immediate protein consumption, from almost none to excessive amounts, the degree of growth of the single kidney, adrenal and ovary left after removal of the other organ in each pair is the same up to five days after the operation. On a 1 per cent protein diet there is no growth of the remaining organs after the first five days. On diets containing from 10 to 57 per cent of protein there is no definite relation between the level of protein consumption and

the rate and degree of growth from five to forty days after the operation. When rats are given a 1 per cent protein diet for ten days before the operation, a continuation of this diet reduces the initial growth of the remaining organs and leads to cessation of growth after the first two days. FROM AUTHORS' SUMMARY.

AVIAN THIAMINE DEFICIENCY. R. L. SWANK, J. Exper. Med. **71**:683, 1940.

The opisthotonos of thiamine deficiency is a manifestation of decerebration due to functional impairment of the neurons which have an inhibitory influence on the lower centers in the brain stem. Leg weakness (when produced by the same deficiency) is due to degeneration of peripheral nerve fibers within the sciatic nerve. Heart failure may be attended by no visible histologic changes, but in many instances necrosis of myocardial fibers occurs.

FROM AUTHOR'S SUMMARY.

FATTY CHANGES IN OXYGEN WANT AND STARVATION. H. ULRICH, Frankfurt. Ztschr. f. Path. **52**:80, 1938.

Guinea pigs were used in the experiments. In the animals kept for a varying period under decreased oxygen pressure, fatty changes were found in the kidneys, in the heart muscle and in the liver. The most severe changes were found after deprivation lasting about forty-eight hours. After this length of time the fat content of these organs decreased. After a still longer period the kidneys and heart muscles showed no fat at all. In starved animals the fatty changes were much less pronounced than in those which were kept under reduced oxygen pressure. The author stressed that in pregnant animals there were less fatty changes than in the control, nonpregnant animals. It is believed that because of the oxygen want the fat depots were depleted and that the fat appeared in the circulating blood. As a result the fat was deposited in those cells and structures which are able to store fat, particularly in the liver, myocardium and kidney. After the fat has disappeared from the depots, the organ fats gradually disappear. In these experiments central necrosis of the liver was often found. It seems that the severity of the necrosis paralleled the severity of the fatty change. O. SAPHIR.

ARTERIOSCLEROSIS PRODUCED BY AMMONIUM HYDROXIDE POISONING. J. VON BALO, Frankfurt. Ztschr. f. Path. **52**:205, 1938.

Rabbits were fed with 50 to 80 cc. of a 0.5 per cent aqueous solution of ammonium hydroxide daily or every second day. This was done twenty-three to one hundred and six times. The author believes that the resulting acidosis caused changes in the aorta wall, characterized by either complete destruction of the muscle fibers or simply severe mucoid degeneration. Later the elastic fibers showed evidence of regeneration, or if the changes were too severe, the necrotic regions were replaced by areas of calcification. These changes of the aorta seemed to be similar to those produced by injections of a solution of epinephrine. The belief is expressed that acidosis also plays a definite role in the causation of human arteriosclerosis because certain diseases which often precede arteriosclerosis, such as nephritis, diabetes mellitus and lead poisoning, have acidosis as a common factor.

O. SAPHIR.

## Pathologic Anatomy

MEDIAL DEGENERATION, CYSTIC VARIETY, IN UNRUPTURED AORTA. A. ROTTINO, Am. Heart J. **19**:330, 1940.

Seven instances of cystic medial degeneration of the aorta, found in a study of 210 aortas, are described. In 4 of these there were also a few to many areas of muscle loss. Cystic degeneration in the latter areas was observed in 2 cases. In all 4 instances other cystic lesions were independent of foci of muscle loss. In 4 vessels the earliest change appeared to be disintegration of elastic lamellae.

The same was observed in 11 of 12 cases of dissecting aneurysm of the aorta. The composite picture of medial degeneration in any aorta appears to consist of a primary lesion plus secondary tears resulting from the focal weakness which it causes. These tears, when significant enough, lay the groundwork for a major rupture of the vessel wall.

FROM AUTHOR'S SUMMARY.

THE SAPHENOUS VALVES IN VARICOSE VEINS. J. E. EDWARDS and E. A. EDWARDS, Am. Heart J. **19**:338, 1940.

The valves in the upper ends of varicose saphenous veins were studied, and the valves of normal veins were examined for comparison. The lesions varied in the different varieties of varicose veins. Most of the varices were either spontaneous or followed phlebitis of the deep veins. In these two groups the valve cusps showed no profound intrinsic lesions. The fundamental lesion was a dilatation of the commissural region, i. e., the portion of the wall between the attachments of the valve cusps. This gave rise to an evagination of the wall and a separation of the cusps. Secondary changes of a reparative nature were seen. These consisted of a growth of fibromuscular tissue on the luminal surface of the dilated commissure. The cusps showed some extrinsic changes dependent on the primary lesion of the wall, such as: relaxation of the cusp with redundancy and kinking; occasionally, rolling of the free margin of the cusp, and, in a few cases of severe involvement, a distal eversion of the cusp. In a smaller number of cases of varicose vein, antecedent deep thrombophlebitis had also attacked the portion of the saphenous vein examined. These cases were few in number. The same destructive changes of the cusp were seen in thrombophlebitis complicating established saphenous varicosities. In some so-called normal veins, early changes were seen similar in nature to those present in varicose veins. It appears that the regurgitation of blood in the upper end of a saphenous vein in the usual variety of varicosity is secondary to a relative insufficiency of the valves dependent on the dilatation of the wall of the vein. Moreover, the study indicates that the cause of varicose veins is to be sought in the disproportion between the venous pressure and the resistance of the wall of the vein. The usual type of varicosity is not caused by local infection or inflammation, thrombophlebitis or spontaneous degeneration of valves.

FROM AUTHORS' SUMMARY.

HISTOGENESIS OF HEPATIC CIRRHOSIS IN CHRONIC FOOD SELENOSIS. R. D. LILLIE and M. I. SMITH, Am. J. Path. **16**:223, 1940.

In rats wheat from seleniferous soil when combined with a low protein, high carbohydrate diet produces well marked nodular cirrhosis of the liver. Associated with this are considerable cellular destruction and phagocytosis of nuclear debris in the follicles of the spleen, and moderate splenic myelosis. High fat, low protein and high protein diets do not completely protect against the action of organic selenium but do greatly delay and decrease the frequency of such effects. Organizing hemorrhage is a frequent and possibly essential stage in the histogenesis of the cirrhosis of food selenium poisoning in rats. The destructive process is continuous, as shown by the presence of scattered, isolated necrotic liver cells and of the hyaline oxyphilic globules derived from them at all the later stages in the process. The cirrhosis produced by organic selenium poisoning does not especially resemble that of cinchophen, copper, silicic acid or phosphorus poisoning.

FROM AUTHORS' SUMMARY.

RENAL LESIONS DUE TO INJECTIONS OF HYPERTONIC SUCROSE SOLUTIONS. W. A. D. ANDERSON and W. R. BETHEA JR., J. A. M. A. **114**:1983, 1940.

Renal lesions followed the intravenous injection of hypertonic solutions of sucrose in 6 patients. The lesions are described and are well illustrated. They

were similar to those observed in animals after experimental injection of sucrose and were characterized by an extreme foamy swelling of the cells lining the convoluted tubules, which in some instances resulted in cell death.

HEMORRHAGIC PERICARDITIS. P. DUBUIS, Ann. d'anat. path. **14**:37, 1937.

An unusual form of hemorrhagic pericarditis was found by the author in an autopsy on a 67 year old man. The pericardial sac was much distended by about 1,500 cc. of old, reddish brown blood. Its inner aspect was lined by a thick, dark brown pseudomembrane, which microscopically was seen to be organizing blood clot. A similar membrane was found on the epicardium. No source for the bleeding could be found. The associated findings were those of decompensation of a hypertrophied heart. The author considers this condition to be a separate entity, resembling so-called pachymeningitis haemorrhagica. [Rupture of either a small area of myomalacia or of malignant mural endocarditis has not been ruled out, however.]

PERRY J. MELNICK.

STRUCTURAL CHANGES OF THE DIGESTIVE TRACT IN AGRANULOCYTOSIS. G. E. ROSENBACH, Beitr. z. path. Anat. u. z. allg. Path. **103**:30, 1939.

Postmortem examination in 50 fatal cases of agranulocytosis revealed gastrointestinal lesions in 36. The lesions were chiefly in the lower part of the ileum and the large intestine and were rare in the stomach and duodenum. Of the several types of lesions, the most frequent and conspicuous was a superficial necrosis of the mucosa, partly or completely circumscribing the bowel, with edema of the submucosa. This necrosis arose in the lymphatic tissue of the intestine and resembled typhoid ulcers. Other lesions were suggestive of those in acute dysentery and uremia. In 1 case, gangrenous necrosis led to perforation with fatal peritonitis. Microscopically, the lesions were characterized by a lessened number or complete absence of polymorphonuclear leukocytes, the exudate consisting chiefly of plasma cells and lymphocytes. The author concludes that the intestinal lesions are due to a blood-borne toxic substance, whose nature and origin are not indicated.

R. J. LEBOWICH.

CHANGES IN THE LIVER IN ACUTE EPIDEMIC HEPATITIS (CATARRHAL JAUNDICE). K. ROHOLM and P. IVERSEN, Acta path. et microbiol. Scandinav. **16**:427, 1939.

Thirty-eight aspiration biopsies were made of the livers of 26 patients with acute jaundice of the catarrhal type. Although the pieces of liver tissue removed were rather small, they revealed: diffuse hepatitis, with destruction of the epithelial cells, more marked in poorly defined foci of varying size; invasion by leukocytes, chiefly small mononuclears; proliferation of connective tissue in the periportal spaces, about the central veins and within the lobules. The interlobular bile ducts were normal. Small hemorrhages were seen here and there where the parenchymatous changes were most pronounced. The hepatitis was marked in the first week after the onset and, as a rule, ran its course within a month after the onset of icterus, without leaving any other trace than a slight or moderate increase in connective tissue. In 3 cases a considerable increase of connective tissue was revealed, suggestive of cirrhosis, but it could not be determined whether some chronic process was present before the onset of the acute hepatitis. In a fatal case there were the changes of subacute hepatic atrophy during the course of apparently acute benign hepatitis.

R. J. LEBOWICH.

## Microbiology and Parasitology

CYTOLOGIC STUDIES ON GLOBI IN LEPROSY. E. V. COWDRY, Am. J. Path. **16**:103, 1940.

Comparison of human leprosy with water buffalo leprosy, rat leprosy and Johne's disease is instructive. Like human leprosy, these diseases have long periods of incubation, the lesions are chronic granulomas, and the bacilli are chiefly intracellular, many of them living in a kind of symbiosis with the cells. Globi in human leprosy resemble in some respects those in water buffalo leprosy. They differ markedly from the rosettes in rat leprosy and the peripheral bodies in Johne's disease. There is no evidence in water buffalo leprosy, rat leprosy or Johne's disease that these distinctive aggregations of organisms are formed extracellularly within the lumens of lymphatics. At least the smaller globi in water buffalo leprosy and all the rosettes and peripheral bodies in rat leprosy and in Johne's disease develop intracellularly in cells of the reticuloendothelial system much as the globi in human leprosy do. FROM AUTHOR'S SUMMARY.

THE TRANSMISSION OF LYMPHOGRANULOMA VENEREUM TO THE GUINEA PIG. A. W. GRACE and F. H. SUSKIND, Am. J. Path. **16**:169, 1940.

The guinea pig is regularly and readily infected with suitable strains of the virus of venereal lymphogranuloma. The induced disease resembles to a certain extent the human form.

THE FOOD HANDLER AS A TRANSMITTER OF AMEBIASIS. A. W. SCHOENLEBER, Am. J. Trop. Med. **20**:99, 1940.

A group of Americans recruited from localities in the United States where the average amebic infection rate is certainly not more than 10 per cent were transported to the island of Aruba, where they lived for a number of years without taking prophylactic measures against the dissemination of amebic infection by carriers. This group lived under conditions which precluded the possibility of acquiring amebic infection from water, flies, sewage or soil contamination of food. After several years of residence under such conditions they showed on examination of stools an infection rate of 25.57 per cent and an incidence of amebic colitis of 36.84 per thousand per annum. Examination of the stools of the food handlers in this camp showed that 33 per cent were ameba carriers. Active measures for the control of dissemination of infection by food handlers were put into effect, and as a result—without any other measures or any changes in the habits or the environment of the group—the infection rate was reduced 50 per cent after one year and 92 per cent after three years. It is realized that this is not a carefully controlled scientific experiment and that it cannot be presented as positive evidence of the transmission of amebiasis by carriers. However, this experience, as well as that of practical workers throughout the tropical world, presents strong presumptive evidence that such transmission occurs. Since, in the opinion of the author, no conclusive proof to the contrary has been presented, he feels justified in continuing the measures against the transmission of infection by carriers.

FROM AUTHOR'S SUMMARY.

SOAP INACTIVATION OF INFLUENZA VIRUS. C. C. STOCK and T. FRANCIS JR., J. Exper. Med. **71**:661, 1940.

The capacity of certain fatty acids at $p_H$ 7.5 to inactivate the virus of epidemic influenza has been demonstrated. Most effective of these are oleic, linolic and linolenic acids. Studies were made of such variables as $p_H$, rate of inactivation and ratios of reactant concentrations, using oleic acid as a prototype of the effective acids. Attempts to recover active virus from inactive mixtures by decrease in $p_H$, dialysis, dilution or addition of calcium chloride solution to inactivated virus

have been unsuccessful. The stability of virus at different hydrogen ion concentrations has been determined. Quantitative comparisons have been made of the immunizing capacities of fully active virus and virus rendered noninfectious by treatment with oleic acid. It was found that the infectious property of the virus is removed but that the immunogenic capacity is essentially unaltered.

FROM AUTHORS' SUMMARY.

ULTRACENTRIFUGATION OF YELLOW FEVER VIRUS. E. G. PICKELS and J. H. BAUER, J. Exper. Med. **71**:703, 1940.

It was possible to study in the ultracentrifuge by optical methods the behavior of yellow fever virus particles directly in the unaltered serum from infected monkeys. The virus showed an extremely high absorption of light in the spectral range of 320 to 440 millimicrons, which seemed to be its intrinsic property. In a 1 cm. thickness of fluid, the small amount of virus present in unaltered infective serum absorbed about as much light (approximately 25 per cent) in the middle of this range as did all the normal serum proteins present in a combined concentration about one thousand times as great. The concentration of virus in the unaltered serum was found to be of the order of 0.00005 Gm. per cubic centimeter. One cubic centimeter of a $10^{-9}$ dilution, which, as has been shown, may constitute a minimal infective dose for monkeys, would contain approximately 10,000 virus particles. The probability that most of the virus particles were in the inactive form is discussed. In infective serum having a viscosity of 14 millipoises the particles sediment with a blurred boundary at rates lying between approximately 10 and $30 \times 10^{-13}$ cm./sec./dyne. Evidence indicates that this spread is the result of an aggregation or association phenomenon. The computations of size are in approximate agreement with those made from ultrafiltration studies. On the assumption that the density of the virus particle is near that of protein, its volume is computed to be at least that of a spherical particle having a diameter of 12 millimicrons. An assumed density of 1.15 Gm. per cubic centimeter yields a diameter of 19 millimicrons if one considers the shape as spherical.

FROM AUTHORS' SUMMARY.

THE $p_H$ STABILITY OF THE VIRUS OF EQUINE ENCEPHALOMYELITIS UNDER VARIOUS CONDITIONS. H. FINKELSTEIN and others, J. Infect. Dis. **66**:117, 1940.

The $p_H$ stability of equine encephalomyelitis virus (Eastern strain) has been studied by means of infectivity titrations in mice.

Virus purified by differential ultracentrifugation was most stable between $p_H$ 7 and 10. Infectivity diminished rapidly in solutions more alkaline than $p_H$ 10, while inactivation in the acid range progressed relatively slowly over a broad region to about $p_H$ 2.0.

Crude chick embryo virus suspensions and suspensions of purified virus to which extracts of noninfected chick embryo tissue had been added showed a similar range of maximum stability between $p_H$ 7 and 10. In addition, a second range of relative stability was exhibited between $p_H$ 3 and 5. Between these acid and alkaline ranges was a region of relatively rapid inactivation—in the neighborhood of $p_H$ 5.5. Outside this range near 5.5 the virus in chick embryo tissue extracts was somewhat more stable than virus in the purified state.

This inactivation at $p_H$ 5.5 was not related solely to hydrogen ion concentration. It was dependent also on a material present in normal and virus-diseased chick embryos. The presence of a factor in guinea pig and mouse brain acting in a similar way but at $p_H$ 4.3 was indicated in experiments with crude suspensions of these tissues diseased with the virus. The nature of the factor and the mode of its action have not yet been determined. The possibility that the material may be an enzyme appears reasonable, and the findings are not in disagreement with it. This possibility can be considered tentatively as a basis for further work.

FROM AUTHORS' SUMMARY.

EFFECT OF SULFAPYRIDINE ON PHAGOCYTOSIS AND DISSOCIATION. R. TUNNICLIFF, J. Infect. Dis. **66**:147, 1940.

Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) diluted 1:1,000 to 1:100,000 in salt solution promotes phagocytosis of greening streptococci, staphylococci and nonencapsulated pneumococci. It stimulates the activity of leukocytes if serum is present, but does not act as opsonin.

Streptococci and pneumococci grown in 1:1,000 sulfapyridine plain broth show by chain formation, and staphylococci by slight colony change, some S→R dissociation which makes the organisms more phagocytable than an equal number in the S phase. Pneumococci grown in 1:1,000 sulfapyridine dextrose broth are not more phagocytable except after several transfers in sulfapyridine dextrose broth, probably on account of the presence of fewer capsules.

One cubic centimeter of a 1:1,000 sulfapyridine solution injected subcutaneously into mice prevents abscess formation by staphylococci injected intraperitoneally. If staphylococci are mixed with mucin, more severe reactions take place, but the results are similar.

Smear preparations from the peritoneal cavities of mice given injections of staphylococci with and without sulfapyridine indicate that, beginning one hour after the administration of sulfapyridine, staphylococci are removed from the peritoneal cavity by phagocytosis. FROM AUTHOR'S SUMMARY.

ACTION OF GASTRIC AND SALIVARY MUCIN ON PHAGOCYTOSIS. R. TUNNICLIFF, J. Infect. Dis. **66**:188, 1940.

Gastric and salivary mucin give a covering to bacteria which prevents their staining vitally and inhibits phagocytosis.

In vivo experiments show that mucin-coated staphylococci are not taken up by leukocytes for two hours following injection, after which time they multiply enormously and kill mice in twenty-four hours. Control mice show phagocytosis of cocci at the end of one hour and recover.

Vitally stained mucoid material in mice given injections of mucin and staphylococci shows unstained mucin-coated cocci as long as three hours after injection. Only stained cocci, uncoated with mucin, are taken up by the polymorphonuclear leukocytes. FROM AUTHOR'S SUMMARY.

PATHOLOGY OF POLIOMYELITIS IN THE COTTON RAT AND WHITE MOUSE. R. D. LILLIE and C. ARMSTRONG, Pub. Health Rep. **55**:718, 1940.

Intracerebral inoculation with the Lansing strain of poliomyelitis virus produces in cotton rats (Sigmodon hispidus hispidus) and white mice (Mus musculus) an inflammatory process characterized by necrosis of nerve cells, polymorphonuclear leukocyte exudation and invasion of necrotic cells, neuronophagia by macrophages, diffuse and focal cellular gliosis, vascular endotheliosis and lymphocyte infiltration of vessel sheaths. In the brain the dorsal portion of the pons shows the greatest involvement, then the medulla, midbrain, thalamus and cerebellar roof nuclei. The cerebral cortex in both species shows relatively little involvement, most in the hippocampus. The corpora striata and the cerebellar cortex show the least involvement. Even with inoculation into the thalamomesencephalic region, the earliest observed lesions are in the spinal cord, in both species.

The process in both species is considered closely similar to poliomyelitis in man and monkeys. In general, the amount of lymphocyte infiltration of vessel sheaths is less in cotton rats than in mice, monkeys or man.

[Peers (*Pub. Health Rep.* **55**:726, 1940) found that neither the initial transfer nor the subsequent passage through 33 cotton rats visibly modified the effects of this strain of poliomyelitis virus in monkeys.] FROM AUTHORS' SUMMARY.

STUDIES ON THE TOXINS AND ANTITOXINS OF CLOSTRIDIUM PERFRINGENS. S. E. STEWART, Pub. Health Rep. **55**:753, 1940.

Clostridium perfringens type A produces at least three different toxin components which are dependent on the type of medium used for culturing the organism. Two of the components are hemotoxins, which can be separated by absorption on dried red blood cell stroma and by filtration. One is lytic for sheep red blood cells, while the other has little action on them after one hour's incubation at 37 C. These two hemotoxins were shown to be antigenically different. Lipoids were found to inhibit the formation of the hemotoxin which is lytic for sheep red blood cells. The hemotoxins may be reversibly inactivated by separating them from the broth in which they are suspended or by bubbling oxygen through the active hemolysins. The hemotoxins may be separated from the broth by filtering the latter through collodion membranes. Activation of the hemolysins can be brought about by introducing substances containing sulfhydryl groups. A nonhemolytic toxin component was found in some of the type A filtrates. It was possible to separate this toxin from the hemolysins by filtering the latter through graded membranes. The "nonspecific toxin" resulting from the cultivation of Cl. perfringens type A in mediums containing from 1 to 2.25 per cent dextrose was found to be neutralized by antitoxins having high antihemolytic titers for the two types of hemolysins. [A good bibliography is supplied.]

FROM AUTHOR'S SUMMARY.

## Immunology

CELLULAR RESPONSE IN THE EARLY STAGES OF THE TUBERCULIN REACTION. R. H. FOLLIS JR., Bull. Johns Hopkins Hosp. **66**:245, 1940.

In the experiments described Follis has repeated as closely as possible the work of Dienes and Mallory, who contended that the tuberculin reaction differs from other forms of acute inflammation in that mononuclear cells predominate at all stages from the beginning of the reaction. Follis' histologic observations on reactions of comparable intensity produced by similar dilutions of tuberculoprotein show that in the tuberculous guinea pig at the site of injection of tuberculoprotein the cellular response in the early stages is predominantly a polymorphonuclear one.

FROM AUTHOR'S SUMMARY.

A TYPE-SPECIFIC ANTIGENIC PROTEIN DERIVED FROM THE STAPHYLOCOCCUS. W. F. VERWEY, J. Exper. Med. **71**:635, 1940.

Chemical extraction of lyophilized and ground staphylococci of type A yielded a type-specific antigenic fraction, which has been shown to be protein. In precipitin tests this fraction reacts in high dilution with homologous immune serum prepared by injecting either the whole organisms or the protein itself into animals. Reactions with serum prepared against heterologous types of staphylococci occur only in low dilutions. The type specificity of this fraction has been found to be entirely independent of the type specificity of the carbohydrate described by Julianelle and Wieghard.

FROM AUTHOR'S SUMMARY.

IMMMUNIZING POTENCY OF ANTIRABIES VACCINES. L. T. WEBSTER and J. CASALS, J. Exper. Med. **71**:719, 1940.

A quantitative method is described for testing the immunizing potency of antirabies vaccines in dogs. Phenolized, single injection canine vaccines from seven manufacturers when administered to dogs according to directions failed to protect them against the least measurable amount of test virus fatal to 50 per cent or more of the controls. Chloroformized vaccines from two of three manufacturers gave under the same conditions equivocal or suggestive results. Commercial chloroformized vaccines in 10 cc. doses, injected intraperitoneally rather than subcu-

taneously into dogs, conferred a significant degree of immunity but proved temporarily irritative to the peritoneum. These results of the use of canine vaccines in dogs parallel closely those already reported in mice.

FROM AUTHORS' SUMMARY.

THE NEUTRALIZATION TEST IN CASES OF LYMPHOGRANULOMA VENEREUM. E. RODANICHE, J. Infect. Dis. **66**:143, 1940.

By means of the intracerebral neutralization test in the white mouse, Rodaniche has been able to demonstrate neutralizing antibodies in the serums of 8 of 9 patients with positive Frei reactions. He has failed to demonstrate such antibodies in the serums of 36 persons with negative Frei reactions.

FROM AUTHOR'S SUMMARY.

REACTION BETWEEN CLOSTRIDIUM WELCHII AND HUMAN SERUM. F. P. O. NAGLER, Brit. J. Exper. Path. **20**:473, 1939.

A reaction is described between the lethal toxin of Clostridium welchii (type A) and normal human serum, in which the serum becomes opalescent. When the opalescent serum is centrifuged, a fatty material rises to the surface. The reaction is specifically inhibited by Cl. welchii antitoxin. The reaction can also be observed if Cl. welchii of any type (A, B, C or D) is grown in a mixture of normal human serum and broth. This cultural reaction has been shown to be specific for Cl. welchii, and it is specifically inhibited by Cl. welchii antitoxin. The lethal toxin of Cl. welchii (type A) can be titrated by means of the reaction, the activity of the toxin bringing about the change in human serum running parallel to its toxicity for mice. Cl. welchii (type A) antitoxin can likewise be titrated, the inhibiting action of the antitoxin in vitro running parallel to its neutralizing action in vivo.

FROM AUTHOR'S SUMMARY.

PRECIPITIN REACTIONS OF PROTEINS. A. KLECZKOWSKI, Brit. J. Exper. Med. **21**:1, 1940.

Horse serum globulin and crystalline egg albumin treated with phenylisocyanate and with formaldehyde give a strong precipitin reaction with rabbit antiserums produced by treatment with corresponding unchanged proteins, but there are certain quantitative differences between their reaction and the reaction of the unchanged proteins. The treatment with phenylisocyanate or with formaldehyde causes some reduction of the affinity toward the antibodies for the corresponding normal proteins. Some quantitative changes of precipitin reaction presumably are due to changes of physical properties of the antigen molecules. Immunization of rabbits with phenylureido–horse serum globulin gave rise to antiserums reacting strongly with phenylureido–horse serum globulin, much less strongly with phenylureido-proteins of other species and only very slightly with normal horse serum globulin.

FROM AUTHOR'S SUMMARY.

RANGE OF ACTION OF THE STAPHYLOLYSINS. J. FORSSMAN, Acta path. et microbiol. Scandinav. **17**:231, 1940.

The pathogenic staphylococci seem to have a wonderful power of producing a long series of different hemolysins, dissolving different kinds of blood corpuscles, and, furthermore, it appears that two antigenic variants of each such lysin occur, in any case as far as the lysins against rabbit, sheep, ox, human and guinea pig blood are concerned. The lysins formerly called $\alpha$ and $\beta$ lysins are not simple lysins but mixtures of lysins, besides which they vary in composition. Because of this, these names are not appropriate and should be replaced by names signifying the lysins' action or at least their chief lytic action, which would mean that $\alpha$ lysin could be named rabbit lysin and $\beta$ lysin hot-cold sheep lysin.

FROM AUTHOR'S SUMMARY.

## Tumors

EFFECTS OF COLCHICINE AND RADIATION ON GROWTH OF NORMAL TISSUES AND TUMORS. A. M. BRUES, B. B. MARBLE and E. B. JACKSON, Am. J. Cancer **38**:159, 1940.

Treatment of tumor-bearing rats and mice with maximal sublethal daily doses of colchicine throughout the life of the animals produces no evidence of retardation of tumor growth or of prevention of recurrences or of metastases after excision of the tumor. Large doses (leading to death in a few days) retard tumor growth. The smaller doses employed, although without effect on tumor growth, are adequate to produce arrest of many mitoses at metaphase. The regression of tumors following large doses of colchicine appears to be correlated with metabolic changes in tissue and with vascular damage. Animals receiving less than these amounts fail to show the fall in tissue ascorbic acid which occurs with the larger doses. Cell multiplication in the course of liver hypertrophy takes place under similar conditions of dosage, frequently at a normal rate, and appears to do so in the complete absence of normal karyokinesis. The administration of colchicine does not enhance or accelerate the effects of radiation in causing tumor regression. It is believed that the apparent arrest of mitosis in the tissues studied is in reality only a prolongation, and in some cases a modification, of certain stages of cell division, which fails to hinder multiplication of cells over a prolonged period.

FROM AUTHORS' SUMMARY.

GROWTH IN WHITE RATS OF EHRLICH-PUTNOKY RAT CARCINOMA. J. PUTNOKY, Am. J. Cancer **38**:191, 1940.

Equal pieces of the Ehrlich mouse carcinoma and the so-called Ehrlich-Putnoky rat carcinoma were implanted by the same technic in Hungarian white rats. The animals were killed at various periods after the inoculation, and the implants were examined histologically. Although the rat's system showed a high degree of resistance to the Ehrlich mouse carcinoma, this very virulent tumor was able in some cases to attain a certain size. With the Ehrlich-Putnoky rat carcinoma, on the other hand, there was hardly any evidence of resistance, and the tumor grew continuously and infiltratively. These observations, together with those in the author's earlier immunity experiments, seem to show that the Ehrlich-Putnoky rat tumor is a substrain of the Ehrlich mouse carcinoma which while living in rats continuously has adapted itself highly to the rat organism. The histologic sections seem to indicate that in the production of immunity against heterologous tumors humoral factors play a large part.

FROM AUTHOR'S SUMMARY.

EFFECT OF THE "SEX HORMONES" ON THE GROWTH OF TRANSPLANTED MAMMARY ADENOFIBROMA IN RATS. F. E. MOHS, Am. J. Cancer **38**:212, 1940.

That estrogen is the endocrine factor determining success in the transplantation of mammary adenofibroma in rats is indicated by the following observations: (*a*) The tumors grow better in females than in males. (*b*) Castration reduces the takes in females. (*c*) Injections of estrogen increase the takes in castrate rats of both sexes. That testosterone has no inhibitory effect on transplanted adenofibroma is indicated by the observations that (*a*) castration has no effect on the percentage of takes in males and (*b*) injections of testosterone do not inhibit adenofibroma in castrates of either sex. If anything, testosterone is slightly stimulatory. The stimulatory effect of estrogen on mammary adenofibroma is probably exerted indirectly through the "mammogenic hormone" of the anterior lobe of the pituitary. The latter hormone appears to be more easily liberated in castrate males than in castrate females, as indicated by the greater percentage of takes in the former. The transplantability and growth rate of adenofibroma may be altered by hormonal means, since this tumor responds like the normal mammary gland to the ovarian and pituitary hormones. The property of unlimited proliferation is, however, inherent in the tumor by virtue of its true neoplastic nature.

FROM AUTHOR'S CONCLUSIONS.

ESTROGEN INJECTIONS IN THE MOUSE. V. SUNTZEFF, R. S. BABCOCK and L. LOEB, Am. J. Cancer **38**:217, 1940.

The hyaline substance which, as a result of administration of large doses of estrogen, is deposited in the uterus, cervix and vagina of the mouse is replaced by ordinary connective tissue after cessation of the injections of estrogen; likewise, the rarefied tissue which develops in certain parts of the vagina and cervix under the influence of this substance subsequently disappears. The replacement of the hyaline substance by normal fibrillar-cellular connective tissue became noticeable one month after cessation of injections of estrogen, had progressed after two months and was about complete after four months. The hyalinization of the tissue is therefore reversible, resembling in this respect the hyalinization which is found around ducts and acini in the mammary gland. The reversion is most readily accomplished in those parts of the uterus where under normal conditions the tendency to the formation of dense collagen structures is least pronounced, and the hyaline persists longest in those places where normally the tendency to the development of dense collagen is greatest. Simultaneously with the return of the stroma of the sex tract to normal conditions, ovulation is resumed in the ovary, and corpora lutea again form. In the mammary gland growth and secretion and carcinoma progress even under conditions in which, as a result of cessation of ovarian function, retrogressive changes take place in the vagina and uterus. In these experiments growth and secretion were accelerated and intensified in mice which had received a series of injections of estrogen during the early period of their life, as compared with nontreated mice. These results are in agreement with those of earlier experiments, in which it was shown that ovarian substances administered during an earlier period of life induce growth changes in the mammary gland which become manifest long after these substances have ceased to act.

FROM AUTHORS' SUMMARY.

RESULTS OF A "FUNCTIONAL TEST" IN A STRAIN OF MICE (C57 BLACK) WITH A LOW INCIDENCE OF BREAST TUMOR. C. C. LITTLE and J. PEARSONS, Am. J. Cancer **38**:224, 1940.

In the strain of mice with a low incidence of cancer of the breast, forced breeding of females provides a means of detecting certain individuals which differ from the rest of the strain in that in them there is a greater tendency to the formation of mammary tumors. The failure of such animals to appear in a fair-sized random sample of the stock (98 females) and their occurrence in 15.0 per cent of another sample of 60 (Bagg) indicate that a substrain in which the tendency to form mammary tumors is relatively higher may have been produced by mutation or by some other process. Forced breeding, which simplifies the reproductive history of female mice by eliminating nursing, brings out certain facts concerning the aging of the reproductive system as follows. At and after 215 to 244 days of age the females usually show: (*a*) decrease in number of young per litter; (*b*) increase in the interval of time between successive litters; (*c*) increase in percentage of young stillborn; (*d*) increase in stillbirths of whole litters as compared with stillbirths of scattered individuals. The "functional test," which involves subjecting animals to a wide range of physiologic activity, is a sound method of bringing out the degree of elasticity of various genetic characteristics. It also helps to detect the incidence of "hidden" mutations which may have occurred and which under ordinary conditions might pass unnoticed. (See also Fekete, E.: *Am. J. Cancer* **38**:234, 1940.)

FROM AUTHORS' SUMMARY.

TRANSPLANTABLE CARCINOMA OF THE RAT BREAST. M. J. EISEN, Am. J. Cancer **39**:36, 1940.

A spontaneous adenocarcinoma of the breast in an inbred female rat of the August strain and its growth under various conditions are described. Subcutaneous, intraperitoneal, intravenous and intraocular transplantation was successful in 100 per cent of the animals of the same inbred strain. Within the normal range of

biologic variability, growth of the transplanted tumors was regular and predictable. In rats given tumor emulsion intravenously the early pulmonary growths were papillary in nature; subsequently cystic changes were prominent. No evidence of immunity to the tumor was observed, indicating that the phenomena of immunity are elicited only when heterozygous animals are utilized for the transplantation of tumors. With a single exception, the tumor failed to grow after subcutaneous, intraperitoneal or intraocular implantation in animals of alien inbred strains but grew irregularly in August rats of related lines. The dose of roentgen radiation required to destroy the tumor in vitro was between 5,000 and 5,500 roentgens.

FROM AUTHOR'S SUMMARY.

STOMACH LESIONS IN RATS KEPT ON DIETS DEFICIENT IN VITAMIN A. L. S. FRIDERICIA and others, Am. J. Cancer **39**:61, 1940.

In four experiments 114 rats were subjected to a diet deficient in vitamin A either intermittently or continuously, while 74 rats were kept on a normal diet as controls. At autopsy, proliferative changes in the mucosal lining of the stomach were found in 91 of the experimental rats (80 per cent) but in only 13 of the controls (18 per cent). In the stomachs of 1 experimental and 1 control rat histologic changes were found which suggested malignant growth. In a fifth experiment 21 rats that survived an exploratory laparotomy after they had been kept for eighteen weeks on alternating A-deficient and normal diets showed the lesions observed when they were killed after having been restored to and maintained on a normal diet for one year. From the results of these experiments it is concluded that vitamin A deficiency must have been in a great measure a determining factor in the production of the gastric changes, though it must be assumed that other factors, as yet unknown, played an important part. The theory proposed in a recent editorial in the *Lancet*, that a virus infection may be instrumental in determining the development of the lesions, is neither confirmed nor refuted by the results of the present experiments.

FROM AUTHORS' SUMMARY.

LIFE EXPECTANCY AND THE MORTALITY FROM CANCER OF THE SKIN AND OF THE LIP. S. PELLER, Am. J. M. Sc. **199**:457, 1940.

At the onset of the disease, carriers of a carcinoma of the skin or of the lip are about as old as the average of all other cancerous patients. At the time of death the patients with cancer of the skin or of the lip are older. The influence on the life expectation and mortality depends on the age at onset. Patients with cancer of the skin or of the lip below 60 years of age in the present material have an increased mortality and a shortened life expectancy as compared with the average population at the same age. Persons with onset of the cancer at ages above 70 have a lower mortality and a higher life expectancy. At the beginning of the "cancer age," at 40, the total group of future carriers of a surface cancer have most probably a future life surplus compared with the total population of the same age. This indicates that the primary internal cancers developing in those who already have or have had surface cancer are not frequent enough to diminish the life expectancy in this group or to frustrate the value of treatment of the surface growths.

FROM AUTHOR'S SUMMARY.

BLOOD ESTERASE IN RATS BEARING ADENOCARCINOMA. E. E. TROESCHER and E. R. NORRIS, J. Biol. Chem. **132**:553, 1940.

A micromethod has been devised for the measurement of the blood esterase activity in Wister rats inoculated in the groin with 0.5 cc. of peritoneal fluid containing cells of adenocarcinoma. In all of the animals inoculated tumors developed. Determinations of esterase activity were made on tail blood at various intervals up to twenty-six days after the inoculation. The results indicate that during the growth of an implanted adenocarcinoma the esterase activity of the blood falls

far below the range of fluctuation of blood esterase values in normal rats. Recession of the tumor in 3 rats was accompanied in each instance by a rise in blood esterase activity toward normal values.

R. J. LEBOWICH.

DISTINCTIVE SUBSTANCE IN RABBIT CARCINOMA. J. G. KIDD, J. Exper. Med. **71**:335 and 351, 1940.

In saline extracts of the Brown-Pearce rabbit carcinoma a substance is regularly present which is capable of fixing complement specifically when mixed with the serum of certain rabbits bearing the tumor or in which the tumor has recently retrogressed. The substance was not demonstrable in extracts of the normal tissues, virus papillomas or uterine cancers of rabbits, nor in extracts of rabbit tissues infected with certain viruses (vaccine virus, virus III, fibroma virus). The serum of normal rabbits, of those immune to a variety of infectious diseases, including syphilis, vaccinia, fibromatosis and virus III, and of others with uterine cancers or virus-induced papillomas failed to fix complement specifically in mixture with extracts containing the antigen of the Brown-Pearce tumor.

The serologically active substance of the Brown-Pearce tumor, a complement-fixing antigen, differs notably from certain other tissue antigens (the Wassermann, Forssman, and organ-specific and species-specific tissue haptens, for example) in the fact that it is not effective after alcoholic extraction of the tissue containing it. Like many of the proteins and viruses, it is inactivated on heating to 65 C. for thirty minutes, and, like them, its activity is lost on treatment with acid (to $p_H$ 4.5 or lower) or alkali (to $p_H$ 11.5 or higher). Filtration and centrifugation experiments disclosed that the antigen passed readily through collodion membranes with average pore diameters of 383 microns and more but was retained completely by those with average pore diameters of 348 microns and less. It was thrown down completely or almost completely on centrifugation at 20,000 revolutions per minute for one hour. The findings indicate that this antigen of the Brown-Pearce tumor has a large and nearly uniform particle size and weight—as large as that of many of the viruses. The findings differentiate it sharply from the generality of "soluble antigens." On direct comparison, the complement-fixing antigen of the Brown-Pearce tumor was found to be similar in a number of its general traits to the serologically active substance of the virus-induced papillomas of rabbits, which in turn is intimately associated or identical with the virus responsible for the papillomas. Extracts of the Brown-Pearce tumor containing the serologically active substance in quantity have given rise to no lesions, however, on injection into normal or tarred rabbits.

FROM AUTHOR'S SUMMARIES.

CANCERS FROM VIRUS PAPILLOMAS OF WILD RABBITS. J. G. KIDD and P. ROUS, J. Exper. Med. **71**:469, 1940.

Some of the naturally occurring virus papillomas of western cottontail rabbits become malignant. The cancers derive from the papilloma cells; that is to say, from elements already rendered neoplastic by the virus and still infected therewith. Papillomas produced with the virus in jack rabbits and snowshoe rabbits become cancerous in the same way and much more frequently, as is the case in domestic rabbits also. To all three species the virus is foreign. The character of the cancers of the wild rabbits is described and the relation of the virus to the cancers discussed on the basis of experimental findings. The facts support the view that the cancers result from virus variation, this in many instances being but slight.

FROM AUTHORS' SUMMARY.

CAUSATIVE AGENT OF A CHICKEN TUMOR. A. CLAUDE and A. ROTHEN, J. Exper. Med. **71**:619, 1940.

The tumor-producing fraction, isolated from chicken tumor I by means of differential centrifugation at high speed, has been investigated as regards its power to absorb ultraviolet rays. A characteristic absorption spectrum was found, with

a maximum at Gilcoke no. 2,575. The absorbing power of the material in that region was largely due to the presence of nucleic acid or of a closely related compound. Inactivation of the purified tumor fraction with ultraviolet rays depressed the absorbing power of the material, especially in the region of 2,600 to 2,500 angstroms. These changes were those which nucleic acid would present under the same conditions. Inactivation of the tumor agent with acid or alkali was accompanied by decomposition of the tumor nucleoprotein and passage of free nucleic acid into solution. Partial or complete inactivation of the tumor agent by heat, at 50 or 65 C., was attended by liberation of nucleic acid of low molecular weight. The parallelism between tumor-producing activity and the integrity of the tumor ribonucleoprotein suggests that the nucleoprotein may be an essential part of the active principle.

FROM AUTHORS' SUMMARY.

ATTEMPTS TO PRODUCE TUMORS IN RATS BY FEEDING CRUDE WHEAT GERM OIL MADE BY PROLONGED ETHER EXTRACTION. HAROLD BLUMBERG, Pub. Health Rep. **55**:531, 1940.

The report by Rowntree and co-workers of the production of tumors by feeding a special wheat germ oil has created great interest. Indeed, preparations of oil from wheat germ are used somewhat for therapeutic purposes, but these refined products were stated to be free from tumor-producing action. However, failures to confirm the results have left the subject in an uncertain position. In the experiments described in this report no intra-abdominal or other tumors occurred, despite the use of the same strains of rats (Buffalo and Wistar) and the same stock diet. Unfortunately, a sample of the oil from Rowntree's laboratory could not be made available, but the wheat germ oil used was prepared by twenty-four hours of ether extraction, following the latest directions of Rowntree and co-workers. Some animals were born, raised and maintained on diet secured directly from the Rowntree laboratory, and a group of animals was also obtained from the same place. In all cases the experiments were continued well beyond the reported maximum induction period for the dosage used.

In view of these consistently negative results it is conceivable that some additional factor may be necessary besides a susceptible strain of rats, the particular stock diet and the specially prepared oil. The induction period sometimes found, thirteen to fifty-four days, is in general much shorter than that required by the most potent hydrocarbon carcinogens when these are injected directly into rats. Furthermore, the induction period shows considerable variation with the same oil dose, from 15 to 111 days with 4 cc. amounts, or 36 to 268 days with 1 cc. amounts. Further investigations are necessary in order to elucidate this problem.

FROM AUTHOR'S DISCUSSION.

SO-CALLED "GRANULOSA" AND "THECA" CELL TUMORS OF THE OVARY. H. F. TRAUT and A. A. MARCHETTI, Surg., Gynec. & Obst. **70**:632, 1940.

Traut and Marchetti were appointed to study the 61 ovarian tumors collected by the Society of Gynecological Pathologists of New York and diagnosed as belonging to the group of neoplasms having their origin in the theca cell–granulosa cell complex. While the work is as yet incomplete, enough information has been obtained to justify a partial report, based on observations of 54 tumors. It was found that Foot's silver stain makes possible the differentiation of theca cells from granulosa cells in most instances. Also, that so-called granulosa cell tumors contain varying amounts of theca cell elements as well, so that pure granulosa cell tumors are rare. Most growths contain from one fourth to one third of their differentiated cells in the form of theca cells. A number had equal representations of the two cell types, while most so-called theca cell tumors also contained granulosa elements in considerable representation. One pure granulosa cell tumor and

4 pure theca cell tumors are described. The authors attempt to outline the life cycle of these tumors and its present relationship to the clinical syndrome they present.

WARREN C. HUNTER.

CHRONIC GASTRITIS IN RELATION TO GASTRIC CARCINOMA. R. WANSER, Beitr. z. path. Anat. u. z. all. Path. **103**:113, 1939.

It is pointed out that Konjetzny based his opinion on the study of material in which it would be difficult to determine whether gastritis preceded or followed the cancer; also that Konjetzny failed to consider properly certain regressive changes found in the gastric mucosa in old age which resemble the atrophic stage of chronic gastritis. Wanser examined over 300 resected specimens from relatively young subjects. In only 8 cases was there pure uncomplicated chronic gastritis; this, however, differed morphologically from that which Konjetzny associated with gastric cancer. Wanser concludes on morphologic grounds that common chronic gastritis is not a precancerous lesion.

UNUSUAL CYSTIC CHANGE IN BOTH OVARIES OF A 16 YEAR OLD GIRL. C. FAHRIG, Beitr. z. path. Anat. u. z. allg. Path. **103**:248, 1940.

Both ovaries weighed about 650 Gm. and were oval and flattened, measuring 18.0 cm. in length, 12.0 cm. in breadth and 6.5 cm. in thickness. They contained innumerable follicular cysts, ranging in size up to that of a cherry; they were filled with clear, watery fluid and separated from each other by either the cyst walls or edematous, swollen septums. The cysts were lined by one or more layers of epithelial cells bounded by a thecal intima. There was no evidence of luteinization. Death resulted from lymphatic leukemia a little more than a year after operation. At autopsy there were no abnormal changes in the uterus and tubes; the endometrium was smooth, pale and of normal thickness; the anterior lobe of the hypophysis was not enlarged but showed a marked increase in cells containing eosinophilic granules. On morphologic grounds and because an anterior pituitary extract containing the gonadotropic factor induced in immature female mice cystic change of the ovaries essentially similar to that observed in his patient, the author concludes that excessive production and hyperactivity of the anterior pituitary follicle-stimulating hormone is responsible for multiple follicular cysts of the human ovary.

R. J. LEBOWICH.

FAILURE TO TRANSMIT MAMMALIAN TUMOR BY CELL-FREE FILTRATES. U. KREIDE and H. KUDICKE, Frankfurt. Ztschr. f. Path. **52**:407, 1938.

Cell-free filtrates of the Brown-Pearce carcinoma were used. In not a single instance did these filtrates produce tumors as seen grossly or after detailed microscopic examination of the lungs, liver, spleen, kidneys, pancreas, adrenals, and skin in the region of the injection.

O. SAPHIR.

EPITHELIAL CYSTS OF THE SKIN. W. NÜRMBERGER, Frankfurt. Ztschr. f. Path. **52**:448, 1938.

One hundred and seventy-eight epithelial cysts of the skin were examined; 121 were epidermoid cysts, 40 were dermoids and 17 were classified as traumatic epithelial cysts. The author stresses the rare finding of a foreign body granuloma as a result of rupture of a squamous cell–lined cyst, with the presence of cholesterol crystals and xanthoma cells. Such granuloma, termed lipophagic foreign body granuloma, has been described, according to the author, only three times. Simple epithelial cell hyperplasia and atypical proliferation of epithelial cells were present in 6 per cent of these cysts. Five benign squamous cell tumors were encountered. In 7 instances the author found squamous cell carcinoma arising in these cysts.

O. SAPHIR.

## Technical

A Silver Carbonate Stain for Oligodendrocytes and Microglia. J. C. McCarter, Am. J. Path. **16**:233, 1940.

A modification of Penfield's method for silver staining of oligodendrocytes and microglia is reported. The method allows use of the tissue fixed in solution of formaldehyde and is easily applied. It has given good results in the author's hands, and it is believed this method should be of value in a neuropathologic laboratory.

From Author's Summary.

Preserved Human Blood. E. J. Gowin and others, J. A. M. A. **114**:850, 855, 858 and 859, 1940.

*Factors Influencing Hemolysis.*—Progressive hemolysis occurs in human blood stored in any of the preservatives studied. The rate of such hemolysis is much greater at 20 C. than at 5 C.

The addition of large quantities of isotonic dextrose solution to blood slows considerably the rate of hemolysis as compared with that in blood stored with little or no added dextrose. The Rous-Turner blood-dextrose-citrate mixture has been so modified that it can safely be given intravenously without discarding the plasma. This modification consists of 10 volumes of blood, 13 volumes of 5.4 per cent aqueous solution of anhydrous dextrose and 2 volumes of 3.2 per cent dihydric sodium citrate in water. Blood stored in the modified blood-dextrose-citrate mixture will hemolyze only one twenty-fifth to one fiftieth as much in thirty days at 5 C. as will blood in sodium citrate alone or in sodium citrate plus sodium chloride. The blood-dextrose-citrate mixture has proved safe and practical for human transfusions and is of distinct advantage in the operation of blood banks with a small volume of transfusions. Hemolysis is less in blood stored in sealed flasks from which the air is completely displaced by the blood mixture than when the blood is exposed to the air. Blood stored in flasks containing air trapped by rubber stoppers hemolyzes no faster than blood exposed to the air in cotton-plugged flasks. Erythrocytes stored in the dextrose-citrate mixture resist destruction by shaking better than do those stored in sodium citrate alone or in citrate-saline mixtures. The initial hemolysis encountered when blood is drawn into large volumes of preservatives can be prevented if the blood is cooled rapidly and uniformly by mixing it with preservatives which have been previously cooled to about 5 C.

*Diffusion of Potassium from Erythrocytes.*—There is progressive diffusion of potassium from human erythrocytes into the plasma during storage. This diffusion is rapid during the first five days but becomes gradually less. A maximum concentration of potassium in the plasma is approached in fifteen to twenty days. The high values of plasma potassium attained in fifteen to thirty days of storage cannot be accounted for by the release of that ion from completely hemolyzed cells. Variations in the content of sodium, chloride, citrate and dextrose in the preservative mixtures or storage at different temperatures and in various atmospheres do not affect the diffusion rate.

*Toxicity of Blood with High Plasma Potassium.*—The high plasma potassium content in blood preserved for thirty days is not toxic when the blood mixture is transfused into human beings at velocities of less than 43.3 cc. per minute. The concentrations of plasma potassium encountered in blood stored for one month are not high enough to cause significant increases in the serum potassium of the recipient.

*Transfusion of Cold Blood.*—A detailed study of 10 patients who were given transfusions of blood mixtures varying from 25 to 15 C. and at velocities from 6.0 to 42.8 cc. per minute revealed no significant lowering in the body temperature, no consistent changes in blood pressure and no untoward clinical symptoms. Preserved blood has been administered without preheating in 568 cases with no reac-

tions which could be attributed to the procedure. The practice of transfusing preserved blood cold is a great convenience in conserving time and prevents untoward reactions involved in the process of heating it. Parenteral fluids other than blood can be administered at room temperature with safety.

FROM AUTHORS' SUMMARIES

THE MICRODETERMINATION OF HEMOGLOBULIN. J. F. BARRETT, Brit. J. Exper. Path. **21**:22, 1940.

The reduced form of the oxidation reduction indicator 2,6-dichlorophenolindophenol is a useful reagent for the detection of blood. In the presence of hydrogen dioxide and blood pigment a red color is produced. A response is obtained with a 1:50,000 dilution of blood. The reaction has been utilized to determine the hemoglobin content of minute quantities of blood. The equivalent of 0.00025 milliliter is required for a determination. FROM AUTHOR'S SUMMARY.

A LIST OF MICROMETHODS FOR THE DETERMINATION OF CALCIUM AND PHOSPHATE. R. S. MANLY, Microchemie **27**:145, 1939.

The author has tabulated seventy-eight recent papers dealing with microchemical determination of calcium and phosphorus, with information concerning the principles on which each procedure is based, the necessary reagents and apparatus, and with the precision and accuracy of each method.

R. J. LEBOWICH.

# Society Transactions

## PATHOLOGICAL SOCIETY OF PHILADELPHIA

*Regular Meeting, Oct. 10, 1940*

J. H. CLARK, *President*

H. L. RATCLIFFE, *Secretary*

**Bilateral Meningioma of the Brain.** WILLIAM P. JENNINGS.

Multiple meningioma is not particularly rare, but its potentialities for invasion of brain tissue and its multiform structure are not widely recognized. A white woman of 56 years had been ill for two years, complaining of slowly progressive weakness, slurred speech and unsteady gait during the first year, after which symptoms were relatively stationary until just before admission. Death occurred twenty days after right frontoparietal craniotomy, due to thrombosis and edema of the brain and congestive heart failure. One tumor, 3 cm. in diameter, was located in the white matter of the right frontal lobe, involving the anterior portion of the caudate nucleus and lying adjacent to the lateral ventricle. A second tumor, 6 cm. in diameter, involved the cortex and white matter of the left frontal lobe and was fixed to the meninges.

The tumors resembled glioma grossly but not histologically. Multiple sections of both tumors were similar, but each tumor was a composite of many elements. Sinusoids and capillaries, together with large, well developed vessels, were identified as pial components. Bony spicules, scattered throughout, seemed to be endosteal derivatives. Interweaving bundles of collagen appeared likewise to be of dural origin, and epithelial-like cells in syncytial sheets, whorled masses and cords corresponded to the so-called arachnoid epithelial rests. Cells containing melanin pigment were noted throughout the tumors. On the basis of the varied types of tissues present, among which representatives of each of the four derivatives of the primitive meningeal tissue can be identified, the tumors can apparently be classified as so-called primitive meningoma.

**Acutely Progressive Hodgkin's Disease.** WILLIAM T. READ JR.

A white man 55 years of age became ill suddenly twenty-eight days before death with headache, weakness and night sweats. The sudden onset was preceded by muscle pains, a cutaneous rash and pruritus and a change in personality. When examined eleven days after the onset he had lost 30 pounds (13.5 Kg.) and had small palpable lymph nodes in the left cervical chain and in both axillas. The cutaneous rash and pruritus had disappeared. The liver was barely palpable, but the spleen could not be felt. The temperature varied from 100 to 104 F. during the illness. Stiffness of the neck developed with lateral nystagmus and palsy of the left side of the face, all of which later disappeared. On the twenty-fourth day of the disease, icterus developed and increased until death. The blood count was: erythrocytes, 2,700,000; leukocytes, 6,700 (segmented neutrophils 51 per cent, staff neutrophils 20 per cent, lymphocytes 12 per cent and mononuclears 17 per cent). Hemoglobin was 8.5 Gm. The culture of the stool contained no pathogens. Repeated cultures of the blood were sterile. Agglutination tests for typhoid bacilli, paratyphoid bacilli, Proteus X19 and brucellas were negative. Autopsy revealed enlarged hepatic and retroperitoneal lymph nodes. The liver contained many small white nodules. The spleen was enlarged and contained numerous nodules. There

were ascites, pleural effusion and edema. On microscopic examination, lymph nodes, liver, spleen and bone marrow contained granulomatous lesions with large numbers of Sternberg-Reed cells, plasma cells and eosinophils.

**Hyperthyroidism Complicated by Tuberculosis of the Adrenals.** L. P. LANG.

A white woman aged 51 years was first seen on March 20, 1940. Her complaints were nervousness and loss of weight. Symptoms indicated hyperthyroidism, and subtotal thyroidectomy was performed on April 11, 1940. A postoperative thyroid crisis developed, and death occurred three days later. Extensive destruction of the adrenals by tuberculosis, early miliary tuberculosis of the liver and lungs and widespread fatty changes in the liver were the significant lesions found at autopsy. It is suggested that the extensive damage to the liver caused by hyperthyroidism and the massive adrenal tuberculosis may have precipitated the thyroid crisis.

**Carcinoma of the Lung Simulating Addison's disease.** M. C. CLYMAN.

A white woman of 59 years presented the following complaints: chyluria and progressive weakness of five years' duration; brown pigmentation of the skin, claimed by patient to be of one and a half years' duration (friends stated it was of at least twenty years' duration); severe pain in the lumbar region, and chronic loss of weight.

The history and examination suggested Addison's disease at two different hospitals, but this was ruled out by normal results from chloride excretion tests and a questionable Negro ancestry. There was no cough, hemoptysis or pain in the chest. The urine contained lipids, casts, erythrocytes and leukocytes. The total blood cholesterol was elevated (esters normal), serum globulin was decreased, phosphatase was increased, and blood pressure was consistently low. Roentgenographic changes of lumbar vertebrae and lung fields could not be interpreted as metastatic tumor. Her condition became progressively worse, and she died with terminal bronchopneumonia. Autopsy revealed numerous pale gray tuberculoid nodules, measuring about 1 mm. in diameter, on the surfaces of the epicardium, pulmonary artery, aorta and pleurae and throughout the pulmonary parenchyma and mediastinal lymph nodes, suggesting miliary tuberculosis, but microscopic sections revealed primary carcinoma of the lung arising from the mucous glands. Skeletal metastases were found.

# Book Reviews

**Dynamics of Inflammation. An Inquiry into the Mechanism of Infectious Processes.** Valy Menkin, Department of Pathology, Harvard University Medical School. Experimental Biology Monographs. Cloth. Pp. 244, with 50 illustrations and 27 tables. Price $4.50. New York: The Macmillan Company, 1940.

After an introductory definition of inflammation and a brief historical survey of the subject, there are 13 additional chapters, in which are discussed the physiology of capillary filtration, the reactions of the capillaries in inflammation and the mechanism of their increased permeability, the migration of leukocytes and the order in which they and other cells appear in the exudate. An examination of the theory of phagocytosis is followed by a consideration of the mechanism of leukocytosis, the relation of inflammation to immunity and the localization of foreign materials in inflamed foci. There are then chapters on allergic and anaphylactic inflammation, the role of lymphatics in inflammation, bacterial invasiveness in relation to resistance and a final recapitulation with conclusions. At the end of each chapter there is a brief and clear summary. The bibliography occupies 26 pages, and there are excellent indexes of authors and subjects.

Menkin's contributions to the subject of inflammation are of undoubted importance. Of the first rank is his isolation from exudates of a substance, named leukotaxine, which increases capillary permeability and enhances the migration of leukocytes. This is a crystalline, doubly refractive, nitrogenous material, probably an intermediary product of the metabolic breaking down of protein. It is not identical with histamine or with the H substance of Lewis. It has nothing to do directly with phagocytosis. Partially reported on but still under investigation is a thermolabile nondiffusible factor of exudate which induces leukocytosis, presumably by a stimulation of the bone marrow to pour out more or less immature leukocytes into the circulating blood.

Much of the material in the monograph is based on Menkin's conception of lymphatic blockade. The network of fibrin in the exudate is accompanied by fibrinous thrombosis in the lymphatics which normally drain the region. This blockage of the lymphatics explains the fixation of particulate matter, microorganisms and proteins in foci of inflammation. Since the blockade is established quickly after the inoculation of Staphylococcus aureus or its products and more slowly after the use of the hemolytic streptococcus, it is inferred that the capacity of pathogenic organisms for dissemination in the body is related to the intensity of the induced local injury rather than to properties of the bacteria. "The patency of regional lymphatics determine the invasiveness of a microorganism." The establishment of the blockade is said to be of significance in resistance because it gives time for the accumulation of leukocytes.

Of additional interest are the studies which indicate that the acidity of an inflamed region is due to faulty metabolism of carbohydrates with local production of lactic acid, that the hydrogen ion concentration determines the nature of the cells of the exudate and that the formation of pus is due to the injury of leukocytes and other cells by acidity below $p_H$ 6.7 or thereabouts. The chapter on allergic and anaphylactic inflammation is well worthy of the rest of the book.

These and other investigations of the author are integrated and correlated with the results obtained by others in the same and neighboring fields, so as to make a consecutive and well oriented discussion of acute exudative inflammation. There is no exposition of the features of other forms of inflammation or of fixed tissue reactions. Thus the title of the book is somewhat more comprehensive than its contents.

Just as pure research furnishes the source material for such applications as industrial research, so do studies of general pathology provide the basis of the investigation of disease in various organs and systems. When the problems of general pathology approach solution, it may be said that the subject of pathology has attained adult stature. Menkin has provided food for this growth toward maturity. His studies are of real importance, and his inferences are for the most part logically drawn. Certainly it is in no sense derogatory to say that they have not been accepted in their entirety by other students of the topic and that opposing views might well have been given more extensive presentation in this monograph. The demonstration of the nature and effects of leukotaxine is convincing, but it will be more so with widespread confirmation. The conception of lymphatic blockade is valid in many forms of inflammation, but that it applies to all forms of the phenomenon in all species is open to question. As long as this is true, the inferences drawn as to bacterial invasiveness may not turn out to be altogether sound.

Nowhere in medicine is teleologic expression given freer play than in reference to inflammation. Menkin has avoided this trap to logical analysis and clear thinking. There is, however, a certain reserve in the statement of his conclusions, wherein many things "seem to be" so, and the reader is often at a loss to know just how sure the author is of his ground.

As with other reports of research work, this volume must be read critically. Nevertheless, it makes excellent and stimulating reading for the pathologist, the physiologist, the biochemist and all others who wish to keep abreast of modern advances in the basic fields of medicine. The style is clear, direct and maintains interest. The book is mechanically good, the tables are clearly arranged and Miss Piotti's drawings are excellent and well reproduced.

**Graduate Medical Education.** Report of the Commission on Graduate Medical Education, 1940. Pp. 304. Chicago: The University of Chicago Press, 1940.

The authors of this book are members of a committee formed in June 1937 by the Advisory Board for Medical Specialties to study the whole problem of graduate medical education. The action was prompted by the existing confusion among physicians, hospitals and medical faculties regarding such education. The commission set itself as an aim not a survey of the present practices but an analysis of the best medical and educational ideals in order to create high standards but not to standardize. The report is based on the concept that medical education is a continuous process extending throughout the physician's lifetime.

The first chapter presents a summary of the three phases of the medical education which follow graduation from the medical school: (1) the internship, which prepares for general practice and provides a basis for future specialization; (2) the residency, which prepares for practice of a specialty and thus constitutes graduate medical education as it is understood at present; (3) the postgraduate medical education, the aim of which is to keep the physician, whether general practitioner or specialist, abreast of current knowledge in his field of practice. Neither the internship nor the courses given as part of postgraduate education can prepare for a specialty. Once this is clearly understood, a great deal of confusion will be avoided.

Three chapters that follow analyze in detail the problems encountered in these three phases of medical education: the functions and responsibilities of the members of the medical staffs of hospitals and of the medical schools, the contents and methods of the different educational experiences, their advantages and disadvantages, their applicability to hospitals of various types and, finally, the special problems of some forms of medical practice.

The fifth chapter gives a brief history and the functions and organization of the specialty boards. The sixth chapter is devoted to a survey of postgraduate medical education in Great Britain. The similarities and differences in that training as compared with the training in this country are interesting and thought provoking. Two appendixes contain tables with statistical data, mostly from

reports by the Council on Medical Education and Hospitals, and brief summaries of some existing plans of postgraduate education.

The material is clearly presented, with a full realization that the problems involved are as yet far from being fully crystallized and that the suggested solutions are in the formative stage. A well organized index and a pleasing exterior add to the value of the book. The work will be of great interest to all who teach medicine in one way or another and to all who learn, and that includes every physician. It will be of special value to members of staffs of hospitals responsible for the training of interns and residents, as well as to hospital administrators.

**Graduate Medical Education in the United States.** Continuation Study for Practicing Physicians, 1937 to 1940. Pp. 243. Price, 60 cents. Chicago: American Medical Association, 1940.

This book consists of reprints, with additions, from *The Journal of the American Medical Association.* The subject is introduced by a review of the progress in graduate medical education since 1913, when the Council on Medical Education created a special committee to investigate the status of graduate teaching. Then follows a review of the facilities to practicing physicians available for continuation study, the organization and administration of these facilities, the methods of instruction, the physician's interest in continuation study, the financial support of graduate education, the clinical conferences, the graduate assemblies and the study courses. The major part of the book, 145 pages, contains a survey of the organization of postgraduate study in all the states of the Union, followed by a review of graduate activities of associated state committees, of the American College of Physicians, of the Social Security and other federal acts, of lending library services and of graduate opportunities for Negro physicians. The last part of the book includes brief chapters on problems of graduate medical education and a report of some of the activities supported by the Commonwealth Fund of New York.

The book is essentially a presentation of the opportunities available for postgraduate education of general practitioners. A well organized index covering 25 pages is appended.

**Pathological Conferences Held at the Cook County Hospital by Dr. R. H. Jaffé.** Edited by Chester C. Guy, M.D. Cloth. Pp. 1164, with one illustration. Price $3.50. Chicago: Cook County Hospital Internes' Alumni Association (Chicago Medical Book Company), 1940.

Richard Herman Jaffé (1888-1937) was known for his broad and practical knowledge of pathologic anatomy, for his ability to correlate clinical and pathologic findings and for the interesting and logical manner in which he dispensed his information. From 1928 until his death in 1937 he conducted a weekly clinical-pathologic conference at the Cook County Hospital, which became very popular, owing to the variety and interesting nature of the material and to Dr. Jaffé's brilliant presentation. Case reports with his comments as given at these conferences were published weekly in the *Bulletin of the Chicago Medical Society.* Five hundred and ninety-six of these reports have been assembled in this volume. Each includes a summary of the history of the patient, the clinical and laboratory observations and the treatment, followed by a description of the observations at autopsy and Dr. Jaffé's discussion. The material includes many examples of all the common diseases and one or more references to rarer ones. The physician, even if his practice is highly specialized, will find much of interest and value in this book. There is a comprehensive index, also a portrait and biography of Dr. Jaffé, with a list of his publications. The volume is bound in waterproof cloth, measures 6 by 9 inches and contains 1,180 pages. It is published by the Cook County Hospital Internes' Alumni Association, not for profit, but as a memorial volume to Dr. Jaffé.

# Books Received

COMPLETE GUIDE FOR THE DEAFENED. A. F. Niemoeller, A.B., M.A., B.S. Foreword by Harold Hays, M.D., F.A.C.S. Cloth. Pp. 256. Price $3. New York: Harvest House, 1940.

INTERNATIONAL HEALTH DIVISION ANNUAL REPORT. 1939. The Rockefeller Foundation. Paper. Pp. 230, illustrated. New York: The Rockefeller Foundation, 1940.

BACILLARY AND RICKETTSIAL INFECTIONS, ACUTE AND CHRONIC. William H. Holmes, professor of medicine, Northwestern University Medical School; chairman, department of medicine, Passavant Memorial Hospital, Chicago. Cloth. Pp. 676. Price, $6. New York: The Macmillan Company, 1940.

DEATH AND DENTISTRY. Martin H. Fischer, M.D., professor of physiology, University of Cincinnati. Cloth. Pp. 242, with 62 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

PRACTICAL HANDBOOK OF THE PATHOLOGY OF THE SKIN: AN INTRODUCTION TO THE HISTOLOGY, PATHOLOGY, BACTERIOLOGY AND MYCOLOGY OF THE SKIN, WITH SPECIAL REFERENCE TO TECHNIQUE. J. M. H. MacLeod, M.A., M.D., F.R.C.P. (London), physician and honorable director of the pathological department of St. John's Hospital for Diseases of the Skin, London; and I. Muende, M.B., B.S., B.Sc. (London), pathologist in charge of outpatients' clinic and lecturer in pathology, St. John's Hospital for Diseases of the Skin, London. Second edition. Cloth. Pp. 415, with 152 illustrations. Price, 42 shillings. New York: Paul B. Hoeber, Inc., 1940.

TABER'S CYCLOPEDIC MEDICAL DICTIONARY INCLUDING A DIGEST OF MEDICAL SUBJECTS — MEDICINE, SURGERY, NURSING, DIETETICS, PHYSICAL THERAPY. Clarence Wilbur Taber and associates. Leatherette. Various pagination, with 273 illustrations. Price, $3.00. Philadelphia: F. A. Davis Company, 1940.

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